

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ASTRAZENECA LP, AKTIEBOLAGET
DRACO, KBI INC. and KBI-E INC.,

Plaintiffs,

v.

BARR LABORATORIES, INC., and
BARR PHARMACEUTICALS, INC.,

Defendants.

C.A. No. _____

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs AstraZeneca LP, Aktiebolaget Draco, KBI Inc. and KBI-E Inc.
(collectively, “Plaintiffs”), by their attorneys, for their complaint against Barr Laboratories, Inc.
and Barr Pharmaceuticals, Inc. (collectively, “Barr”), allege as follows:

The Parties

1. Plaintiff AstraZeneca LP is a limited partnership organized and existing under the laws of the State of Delaware, and has its principal place of business at 1800 Concord Pike, Wilmington, Delaware 19850-5437.

2. Plaintiff Aktiebolaget Draco is a corporation organized and existing under the laws of Sweden and has its principal place of business at Lund, S-221 00, Sweden.

3. Plaintiff KBI Inc. (“KBI”) is a Delaware corporation having its principal place of business at Whitehouse Station, New Jersey.

4. Plaintiff KBI-E Inc. (“KBI-E”) is a Delaware corporation having its principal place of business at Wilmington, Delaware.

5. Upon information and belief, Defendant Barr Laboratories, Inc. (“Barr Laboratories”) is a corporation organized and existing under the laws of the State of Delaware and has a principal place of business at 223 Quaker Road, Pomona, New York 10970. Barr Laboratories does business in the State of Delaware.

6. Upon information and belief, Defendant Barr Pharmaceuticals, Inc. (“Barr Pharmaceuticals”) is a corporation organized and existing under the laws of the State of Delaware and has a principal place of business at 223 Quaker Road, Pomona, New York 10970. Barr Pharmaceuticals does business in the State of Delaware. Barr Pharmaceuticals is the parent of Barr Laboratories, and Barr Laboratories is a wholly-owned subsidiary of Barr Pharmaceuticals.

7. Upon information and belief, Barr Laboratories and Barr Pharmaceuticals collaborated in the research and development of Barr’s Abbreviated New Drug Application (“the Barr ANDA”) No. 90-379 for budesonide enteric coated capsules, 3 mg, continue to collaborate in seeking approval of that application from the Food and Drug Administration (“FDA”), and intend to collaborate in the commercial manufacture, marketing, and sale of budesonide products (“the Barr ANDA product”), in the event the FDA approves the Barr ANDA.

Jurisdiction and Venue

8. This is a civil action for patent infringement arising under the patent laws of the United States, Title 35 of the United States Code, for infringement of United States Patent Nos. 6,423,340 (“the ’340 patent”) and 5,643,602 (“the ’602 patent”). This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

9. Barr Laboratories is subject to personal jurisdiction in this judicial district by virtue of, *inter alia*, its incorporation in Delaware, its conduct of business in Delaware, and having availed itself of the rights and benefits of Delaware law.

10. Barr Pharmaceuticals is subject to personal jurisdiction in this judicial district by virtue of, *inter alia*, its incorporation in Delaware, its conduct of business in Delaware, and having availed itself of the rights and benefits of Delaware law.

11. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

Claim I for Patent Infringement

12. Plaintiffs reallege paragraphs 1 through 11 above as if fully set forth herein.

13. On July 23, 2002, the United States Patent and Trademark Office duly and legally issued the '340 patent, entitled "Method For The Treatment Of Inflammatory Bowel Diseases." A true and correct copy of the '340 patent is attached hereto as Exhibit A.

14. Aktiebolaget Draco is the owner of the '340 patent, which discloses and claims, *inter alia*, methods for treating inflammatory bowel diseases.

15. KBI and KBI-E have rights in the United States under the '340 patent. AstraZeneca LP is the holder of approved New Drug Application ("NDA") 21-324 under Section 505(a) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for an oral budesonide product marketed under the trademark ENTOCORT® EC.

16. The use of ENTOCORT® EC is covered by the claims of the '340 patent, and Plaintiffs have the right to enforce the '340 patent.

17. Upon information and belief, Barr Laboratories submitted the Barr ANDA to the FDA under § 505(j) of the FFDCA, 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, offer for sale and sale of a generic version of ENTOCORT® EC before the expiration of the '340 patent.

18. On or about April 11, 2008, Plaintiffs AstraZeneca LP and Aktiebolaget Draco received a letter dated April 9, 2008, stating that Barr Laboratories had filed the Barr

ANDA seeking approval to manufacture, use, and sell a generic version of ENTOCORT[®] EC before the expiration of the '340 patent. The letter purports to notify AstraZeneca LP and Aktiebolaget Draco that the Barr ANDA was submitted with a certification pursuant to Section 505(j)(2)(B)(i) of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV certification") that Barr's manufacture, use, or sale of the Barr ANDA product will not infringe any claims of the '340 patent, that the '340 patent is invalid, and/or that the '340 patent is unenforceable.

19. Upon information and belief, Barr Pharmaceuticals and Barr Laboratories collaborated in the research and development of Barr Laboratories' ANDA seeking approval to manufacture, use, and sell a generic version of ENTOCORT[®] EC before the expiration of the '340 patent, continue to collaborate in seeking approval of that application from the FDA, and intend to collaborate in the commercial manufacture, marketing and sale of a generic version of ENTOCORT[®] EC in the event the FDA approves the Barr ANDA.

20. Upon information and belief, Barr Pharmaceuticals participated in, contributed to, aided, abetted, and/or induced the submission of the Barr ANDA and its Paragraph IV certification to the FDA.

21. Defendants have infringed the '340 patent under 35 U.S.C. § 271(e)(2)(A) by virtue of their filing the Barr ANDA with a Paragraph IV certification and seeking FDA approval of the Barr ANDA prior to expiration of the '340 patent.

22. The commercial manufacture, use, sale, offer to sell, or importation of the Barr ANDA product would infringe the '340 patent.

23. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of the Barr ANDA be a date that is not earlier than the expiration of the '340 patent, or any later expiration of exclusivity for the '340 patent to which Plaintiffs become entitled.

24. Plaintiffs will be irreparably harmed if Barr Laboratories and Barr Pharmaceuticals are not enjoined from infringing or actively inducing or contributing to infringement of the '340 patent. Plaintiffs do not have an adequate remedy at law.

Claim II for Patent Infringement

25. Plaintiffs reallege paragraphs 1 through 24 above as if fully set forth herein.

26. On July 1, 1997, the United States Patent and Trademark Office duly and legally issued the '602 patent, entitled "Oral Composition For The Treatment Of Inflammatory Bowel Diseases." A true and correct copy of the '602 patent is attached hereto as Exhibit B.

27. Aktiebolaget Draco is the owner of the '602 patent, which discloses and claims, *inter alia*, oral compositions for treating inflammatory bowel diseases.

28. KBI and KBI-E have rights in the United States under the '602 patent. AstraZeneca LP is the holder of approved NDA 21-324 under Section 505(a) of the FDCA, 21 U.S.C. § 355(a), for an oral budesonide product marketed under the trademark ENTOCORT[®] EC.

29. ENTOCORT[®] EC is covered by the claims of the '602 patent. Plaintiffs have the right to enforce the '602 patent.

30. Upon information and belief, Barr Laboratories submitted the Barr ANDA to the FDA under § 505(j) of the FDCA, 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, offer for sale, and sale of a generic version of ENTOCORT[®] EC before the expiration of the '602 patent.

31. On or about April 11, 2008, Plaintiffs AstraZeneca LP and Aktiebolaget Draco received a letter dated April 9, 2008, stating that Barr Laboratories had filed the Barr ANDA seeking approval to manufacture, use, and sell a generic version of ENTOCORT[®] EC

before the expiration of the '602 patent. The letter purports to notify AstraZeneca LP and Aktiebolaget Draco that the Barr ANDA was submitted with a Paragraph IV certification that Barr's manufacture, use, or sale of the Barr ANDA product will not infringe any claims of the '602 patent, that the '602 patent is invalid, and/or that the '602 patent is unenforceable.

32. Upon information and belief, Barr Pharmaceuticals and Barr Laboratories collaborated in the research and development of Barr Laboratories' ANDA seeking approval to manufacture, use and sell a generic version of ENTOCORT[®] EC before the expiration of the '602 patent, continue to collaborate in seeking approval of that application from the FDA, and intend to collaborate in the commercial manufacture, marketing and sale of a generic version of ENTOCORT[®] EC in the event the FDA approves the Barr ANDA.

33. Upon information and belief, Barr Pharmaceuticals participated in, contributed to, aided, abetted, and/or induced the submission of the Barr ANDA and its Paragraph IV certification to the FDA.

34. Defendants have infringed the '602 patent under 35 U.S.C. § 271(e)(2)(A) by virtue of their filing the Barr ANDA with a Paragraph IV certification and seeking FDA approval of the Barr ANDA prior to expiration of the '602 patent.

35. The commercial manufacture, use, sale, offer to sell, or importation of the Barr ANDA product would infringe the '602 patent.

36. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4) including an order of this Court that the effective date of the approval of the Barr ANDA be a date that is not earlier than the expiration of the '602 patent, or any later expiration of exclusivity for the '602 patent to which Plaintiffs becomes entitled.

37. Plaintiffs will be irreparably harmed if Barr Laboratories and Barr Pharmaceuticals are not enjoined from infringing or actively inducing or contributing to

infringement of the '602 patent. Plaintiffs do not have an adequate remedy at law.

Prayer for Relief

WHEREFORE, Plaintiffs seek the following relief:

- A. A judgment that Barr Laboratories and Barr Pharmaceuticals have infringed the '340 and '602 patents under 35 U.S.C. § 271(e)(2)(A);
- B. An order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any FDA approval of the Barr ANDA be not earlier than the expiration date of the '340 and '602 patents or any later expiration of exclusivity for these patents to which Plaintiffs are or become entitled;
- C. A permanent injunction restraining and enjoining Barr Laboratories and Barr Pharmaceuticals and their officers, agents, servants and employees, and those persons in active concert or participation with any of them, from making, using, selling, offering to sell, or importing the product described in the Barr ANDA;
- D. A judgment declaring that the manufacture, use, sale, offer to sell, or importation of the product described in the Barr ANDA would constitute infringement of the '340 and '602 patents, or inducing or contributing to such conduct, by Barr Laboratories and Barr Pharmaceuticals pursuant to 35 U.S.C. § 271 (a), (b) and/or (c);
- E. A finding that this is an exceptional case, and an award of attorneys' fees in this action pursuant to 35 U.S.C. § 285;
- F. Costs and expenses in this action; and
- G. Such further and other relief as this Court determines to be just and proper.

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EXHIBIT A

US006423340B1

(12) **United States Patent**
Ulmius(10) **Patent No.:** **US 6,423,340 B1**
(45) **Date of Patent:** **Jul. 23, 2002**(54) **METHOD FOR THE TREATMENT OF
INFLAMMATORY BOWEL DISEASES**(75) Inventor: **Jan Ulmuis, Lund (SE)**(73) Assignee: **Aktiebolaget Draco, Sodertalje (SE)**(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.(21) Appl. No.: **09/159,301**(22) Filed: **Sep. 23, 1998****Related U.S. Application Data**(63) Continuation of application No. 08/853,142, filed on May 8,
1997, now abandoned, which is a continuation of application
No. 08/240,078, filed on May 9, 1994, now Pat. No. 5,643,
602, which is a continuation of application No. 07/855,623,
filed as application No. PCT/SE90/00738 on Nov. 15, 1990,
now abandoned.(30) **Foreign Application Priority Data**

Nov. 15, 1990 (SE) 8903914

(51) **Int. Cl.**⁷ **A61K 9/52; A61K 9/22;**
..... **A61P 1/00**(52) **U.S. Cl.** **424/457; 424/468; 424/490;**
..... **514/925; 514/964**(58) **Field of Search** **424/462, 457,**
..... **424/468, 490; 514/964, 925**(56) **References Cited****U.S. PATENT DOCUMENTS**

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Primary Examiner—Edward J. Webman
(74) *Attorney, Agent, or Firm*—White & Case LLP(57) **ABSTRACT**

Described herein are methods comprising the oral administration of budesonide for the treatment of ulcerative colitis and Crohn's colitis in its active phase. The methods can also be applied as relapse preventing therapy for Crohn's colitis in its chronic phase and Crohn's disease in the small intestine.

14 Claims, No Drawings

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**METHOD FOR THE TREATMENT OF
INFLAMMATORY BOWEL DISEASES**

This application is a continuation of application Ser. No. 08/853,142, filed May 8, 1997, abandoned, which is a continuation of application Ser. No. 08/240,078, filed May 9, 1994, now U.S. Pat. No. 5,643,602 and which is a continuation of application Ser. No. 07/855,623, filed Apr. 30, 1992 abandoned, which is a 371 of International application PCT/SE90/00738, filed Nov. 15, 1990.

FIELD OF THE INVENTION

The present invention relates to oral pharmaceutical compositions for use in the treatment of inflammatory bowel diseases and the use of certain glucocorticosteroids in the preparation of pharmaceutical compositions for the treatment by the oral route of certain inflammatory bowel diseases.

BACKGROUND OF THE INVENTION

Inflammatory bowel disease is the term generally applied to two diseases, namely ulcerative colitis and Crohn's disease.

Ulcerative colitis is a chronic inflammatory disease of unknown aetiology afflicting only the large bowel and, except when very severe, limited to the bowel mucosa. The course of the disease may be continuous or relapsing, mild or severe. It is curable by total colectomy which may be needed for acute severe disease or chronic unremitting disease. Most patient with ulcerative colitis are managed medically rather than surgically.

Crohn's disease is also a chronic inflammatory disease of unknown aetiology but, unlike ulcerative colitis, it can affect any part of the bowel. Although lesions may start superficially, the inflammatory process extends through the bowel wall to the draining lymph nodes. As with ulcerative colitis, the course of the disease may be continuous or relapsing, mild or severe but, unlike ulcerative colitis it is not curable by resection of the involved segment of bowel. Most patients with Crohn's disease come to surgery at some time, but subsequent relapse is common and continuous medical treatment is usual.

For treatment of acute attacks of ulcerative colitis, glucocorticosteroids such as prednisone or prednisolone acetate are almost invariably used and given by mouth for the average acute attack or relapse, or locally, by enema.

After remission has been achieved, sulphasalazine is the maintenance treatment of choice in treating ulcerative colitis. This drug, however, has a significant number of side effects chiefly due to absorption of the sulphapyridine moiety from the colon. Recently compounds which contain only 5-aminosalicylic acid have been developed; these are as effective as sulphasalazine and do not have the sulphapyridine side effects but do have side effects of their own, notably diarrhoea.

Glucocorticosteroids are, however, not used for maintenance of remission in ulcerative colitis; doses that do not produce unacceptable side effects are ineffective, and patients who need chronic high dose glucocorticosteroids for control of their disease almost invariably are treated by colectomy.

As with ulcerative colitis, glucocorticosteroids are the treatment of choice for severe active Crohn's disease, but ideally only to achieve remission, after which they should be stopped. However, all too frequently the disease does not

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satisfactorily remit, and glucocorticosteroids may be necessary to maintain control of symptoms.

Sulphasalazine is also useful in less severe cases, particularly for disease involving the colon.

Very often in Crohn's disease, however, primary medical treatment of the disease process is ineffective, and only symptomatic treatment is of value i.e. analgesics for pain and opiates for diarrhoea. Most patients eventually require surgery.

DISCLOSURE OF THE INVENTION

Our studies indicate that the compositions according to the present invention may advantageously be used in the treatment of ulcerative colitis including idiopathic proctitis and certain aspects of Crohn's disease by the oral route.

In ulcerative colitis the compositions can be used for the treatment of both active and chronic continuous disease and for relapse preventing treatment (i.e. maintenance therapy once remission has been achieved).

In Crohn's disease the compositions can be used for the treatment of Crohn's colitis in its active phase and for relapse preventing therapy (i.e. maintenance therapy once remission has been achieved), and for the treatment of the small intestine for relapse preventing treatment (i.e. maintenance therapy).

It has been found that the diseases defined above can be treated using the anti-inflammatory steroids

(22RS)-16 α ,17 α -butylidenedioxy-11 β ,21-dihydroxypregna-1,4-diene-3,20-dione [I],
the 22R-epimer of [I],
(22RS)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione [II],
the 22R-epimer of [II],
(22RS)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione [III],
the 22R-epimer of [III],
(22RS)-21-acetoxy-16 α ,17 α -butylidenedioxy-11 β -hydroxy-pregna-1,4-diene-3,20-dione [IA],
the 22R-epimer of [IA],
(22RS)-21-acetoxy-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-pregna-1,4-diene-3,20-dione [IIA],
the 22R-epimer of [IIA],
(22RS)-21-acetoxy-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-pregna-1,4-diene-3,20-dione [IIIA],
the 22R-epimer of [IIIA],
(22RS)-16 α ,17 α -butylidenedioxy-11 β ,21-dihydroxypregna-4-ene-3,20-dione [IV],
the 22R-epimer of [IV],
(22RS)-16 α ,17 α -pentylidenedioxy-11 β ,21-dihydroxypregna-4-ene-3,20-dione [V],
the 22R-epimer of [V],
(22RS)-21-acetoxy-16 α ,17 α -butylidenedioxy-11 β -hydroxypregna-4-ene-3,20-dione [IVA],
the 22R-epimer of [IVA],
(22RS)-21-acetoxy-16 α ,17 α -pentylidenedioxy-11 β ,21-dihydroxypregna-4-ene-3,20-dione [VA],
the 22R-epimer of [VA],
methyl (20RS)-16 α ,17 α -butylidenedioxy-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate [VI],
the 20R-epimer of [VI],
methyl (20RS)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate [VII],
the 20R-epimer of [VII],

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methyl (20RS)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate [VIII],
the 20R-epimer of [VIII],
methyl (22RS)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3,20-dioxopregna-1,4-diene-21-oate [IX] and
the 22R-epimer of [IX].

Compound [I] has the approved name "budesonide".

Compound [I] and its 22R-epimer are particular preferred compounds.

Budesonide and compounds [II], [III], [IA], [IIA] and [IIIA] are described and claimed in Swedish Patent Specification 378 109. Budesonide is known to have an anti-inflammatory activity and, compared to prednisone, prednisolone and other glucocorticosteroids, an advantageous ratio between local and systemic effect when administered topically to the skin or to the lungs by inhalation.

Budesonide is a potent steroid, which is successfully used when locally treating (via aerosol) asthma and rhinitis. Also controlled trials of budesonide enema for locally treating proctitis and distal ulcerative colitis are in progress (Danielsson Å et al: A controlled randomized trial of budesonide versus prednisolone retention enemas in active distal ulcerative colitis, *Scand. J. Gastroenterol.* 22:987-992, 1987 and Danielsson Å et al: Controlled trial of budesonide enema and placebo in proctitis and distal ulcerative colitis, *Scand. J. Gastroenterol.* 24, supplement 159:88). The use of oral budesonide in the treatment of small bowel Crohn's disease in its active phase has been described (Wolman S L: Use of oral budesonide in a patient with small bowel Crohn's disease and previous pseudotumor cerebri secondary to steroids. *Scand. J. Gastroenterol.* 24, Supplement 158:146-147).

The characteristic profile of budesonide when used for the treatment of these diseases is a high anti-inflammatory effect at the place of application but a low degree of unwanted systemic glucocorticoid side effects. The low degree of systemic side effects of budesonide is a result of a high first pass liver metabolism transferring budesonide into substantially less active metabolites.

Especially the 22R-epimer of budesonide seems to be very promising in the treatment of inflammatory bowel diseases as hereinbefore defined when orally administered because, compared to budesonide it is more potent, is more rapidly metabolised by the liver and thus less available in the systemic circulation and thereby causing less unwanted systemic effects.

The 22R-epimers of compounds [I], [II], [III], [IA], [IIA] and [IIIA] are described and claimed in Swedish Patent Specification 378 110.

Compounds [IV], [V], [IVA], [VA] and the 22R-epimers thereof are described and claimed in European Patent Specification 54010.

Compounds [VI], [VII], [VIII] and the 20R-epimers thereof are described and claimed in European Patent Application 143 764.

Compound [IX] and the 22R-epimer thereof are described and claimed in European Patent Application 232 690.

We have surprisingly found that the above identified glucocorticosteroids administered by the convenient oral route are of great potential benefit in the treatment of inflammatory bowel diseases as hereinbefore defined.

The above mentioned compounds thus potentially represents a very significant advance over other glucocorticosteroids which exert their effects systemically and other drugs

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previously used for the management of Crohn's disease, particularly in avoiding the systemic side effects normally associated with glucocorticosteroid therapy. The high first pass liver metabolism of the drug renders possible its safe use in the maintenance therapy of the disease as well as achieving remission in the acute phase. Although Crohn's disease is not a very common condition, it is a chronic and often debilitating disorder that can benefit from a safer and more effective treatment.

In ulcerative colitis, the drug may help to reduce the number of patients having to undergo surgery and in addition, its lack of systemic effects makes it possible to use the drug for maintenance therapy once remission has been achieved.

The invention therefore provides pharmaceutical compositions comprising the glucocorticosteroids hereinbefore defined for use in the treatment by the oral route of bowel diseases as hereinbefore defined.

The invention also provides the use of the glucocorticosteroids as hereinbefore defined in the preparation of pharmaceutical compositions for the treatment by the oral route of bowel diseases as hereinbefore defined.

The invention further provides a method of treatment of bowel diseases as hereinbefore defined wherein an effective dose of a glucocorticosteroid as hereinbefore defined is administered by the oral route to a human or animal subject suffering from said bowel disease.

In order for the oral composition containing the glucocorticosteroids as hereinbefore defined to be applicable for the treatment of the bowel diseases as hereinbefore defined the composition must be adjusted to this particular purpose. The adjusted composition is a further aspect of the present invention, and it can be used generally when treating ulcerative colitis and Crohn's disease.

The transit time through the gastro-intestinal canal for different dosage forms are rather well known. When the dosage form has been emptied from the stomach the transit through the small intestine takes 3 to 5 hours. The residence time in the large intestine is considerably longer, 25 to 50 hours. Ideally, as long as the dosage form remains in the stomach no release should occur. If Crohn's disease in small intestine is going to be treated the release should continue during about 5 hours after the dosage form has left the stomach. If the large intestine is going to be treated the release should ideally start at caecum, and continue for up to 50 hours.

The present invention utilizes pharmaceutical formulation techniques to provide compositions of a glucocorticosteroid for treating the inflammatory diseases of the bowel as hereinbefore defined. The glucocorticosteroid must have a chance to reach the inflamed part of the bowel in sufficient concentration and for a sufficient long time to exert its local action, in the case of Crohn's disease the whole bowel or only the small intestine and in the case of ulcerative colitis the caecum, colon and the rectum.

A multiple unit composition in a capsule has been found suitable for fulfilling the above-mentioned demands. In ulcerative colitis, the composition should be formulated so that the glucocorticosteroid is released preferentially during the passage of the colon. In Crohn's disease in the ileum the composition should be formulated so that the glucocorticosteroid is released preferentially during the Passage of the small intestine. This can be accomplished by enteric and/or slow release coating of the units containing the glucocorticosteroid. Such formulations of glucocorticosteroids are novel.

The dosage range for treatment of the bowel diseases as hereinbefore defined is suitably 2-20 mg divided into 1 to 4 doses during a 24-hour period.

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DETAILED DESCRIPTION

The units will have a size between 0.3 and 5 mm, preferably a size between 0.5 and 2 mm. The units will be administered in hard gelatine capsules, the size of which will depend on the dose administered.

Each unit comprises a core, a first layer on the core and a second layer on the first layer.

The core consists of a non-pareil seed to which the glucocorticosteroid is applied or a seed in which the glucocorticosteroid is homogeneously distributed. The excipients used to prepare the seeds comprise one or more of pharmaceutically acceptable materials, e.g. sugar, starch, microcrystalline cellulose, waxes and polymeric binding agents.

The first Layer on the non-pareil seeds comprises the glucocorticosteroid and a water-soluble or water-insoluble polymer which acts both as binder for the glucocorticosteroid and as a rate-limiting layer for release of the glucocorticosteroid. Such polymers may be selected from cellulose derivatives, acrylic polymers and copolymers, vinyl polymers and other high molecular polymer derivatives or synthetic polymers such as methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, ethylcellulose, cellulose acetate, polyvinyl pyrrolidone, polyvidone acetate, polyvinyl acetate, polymethacrylates and ethylene-vinyl acetate copolymer or a combination thereof. Preferred film-forming polymers are ethylcellulose or copolymers of acrylic and methacrylic acid esters (Eudragit N E, Eudragit R L, Eudragit RS) in aqueous dispersion form.

The first optionally rate-limiting layer on the seeds with homogeneously distributed glucocorticosteroid comprises a water insoluble polymer or a mixture of water insoluble polymers or a mixture of water soluble and water insoluble polymers mentioned above.

The polymers in the second layer may be selected from the group of anionic carboxylic polymers suitable for pharmaceutical purposes and being soluble with difficulty at a low pH but being soluble at a higher pH, the pH limit for solubility being in the interval of pH 4 to pH 7.5, said group comprising cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate and acrylic acid polymers e.g. partly esterified methacrylic acid-polymers such as Eudragit L, Eudragit L100-55 and Eudragit S. These polymers may be used alone or in combination with each other or in combination with water insoluble polymers mentioned before. Preferred polymers are the Eudragits in aqueous dispersion form. The anionic carboxylic polymer comprises 25 to 100% of the total polymer content.

The coatings may optionally comprise other pharmaceutically acceptable materials which improve the properties of the film-forming polymers such as plasticizers, anti-adhesives, surfactants, and diffusion-accelerating or diffusion-retarding substances.

Suitable plasticizers comprise phthalic acid esters, triacetin, dibutylsebacate, monoglycerides, citric acid esters and polyethyleneglycols. Preferred plasticizers are acetyltributyl citrate and triethyl citrate.

Suitable antiadhesives comprise talc and metal stearates.

The amount of the first coating applied on the units is normally in the range between 0.5% and 30% by weight, preferably between 1% and 15%. This amount includes in the relevant case the weight of the steroid as well. The amount of the second coating applied on the units is normally in the range between 1% and 50% by weight, pref-

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erably between 2% and 25%, calculated on the weight of the coated units. The remainder constitutes the weight of the seed.

The preparation of the controlled release pellet formulation according to the present invention is characterized in that a non-pareil seed is enclosed in a layer of a glucocorticosteroid as hereinbefore defined and a water soluble or water insoluble polymer or a seed with homogeneously distributed glucocorticosteroid as hereinbefore defined is optionally enclosed in a layer of a water insoluble polymer or a mixture of water insoluble polymers or a mixture of water soluble or water insoluble polymers which in turn is enclosed in a membrane of a film-forming anionic carboxylic polymer or a mixture of a film-forming anionic carboxylic polymer and a water insoluble polymer which permits release of the glucocorticosteroid as hereinbefore defined in a manner set out below.

The controlled release pellet formulation according to this invention is thus characterized in that the pellet comprises i) a core consisting of a non-pareil seed or a seed in which a glucocorticosteroid as defined below is homogeneously distributed and

ii) in case of a core consisting of a non-pareil seed, a layer of

a) a glucocorticosteroid selected from the group consisting of (22RS)-16 α ,17 α -butyridenedioxy-11 β ,21-dihydroxypregna-1,4-diene-3,20-dione [I], the 22R-epimer of [I], (22RS)-16 α ,17 α -butyridenedioxy-9 α -fluoro-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione [II], the 22R-epimer of [II], (22RS)-16 α ,17 α -butyridenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione [III], the 22R-epimer of [III], (22RS)-21-acetoxy-16 α ,17 α -butyridenedioxy-11 β -hydroxypregna-1,4-diene-3,20-dione [IA], the 22R-epimer of [IA], (22RS)-21-acetoxy-16 α ,17 α -butyridenedioxy-9 α -fluoro-11 β -hydroxy-pregna-1,4-diene-3,20-dione [IIA], the 22R-epimer of [IIA], (22RS)-21-acetoxy-16 α ,17 α -butyridenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-pregna-1,4-diene-3,20-dione [IIIA], the 22R-epimer of [IIIA], (22RS)-16 α ,17 α -butyridenedioxy-11 β ,21-dihydroxypregn-4-ene-3,20-dione [IV], the 22R-epimer of [IV], (22RS)-16 α ,17 α -pentyridenedioxy-11 β ,21-dihydroxypregn-4-ene-3,20-dione [V], the 22R-epimer of [V], (22RS)-21-acetoxy-16 α ,17 α -butyridenedioxy-11 β -hydroxypregn-4-ene-3,20-dione [IVA], the 22R-epimer of [IVA], (22RS)-21-acetoxy-16 α ,17 α -pentyridenedioxy-11 β -hydroxypregn-4-ene-3,20-dione [VA], the 22R-epimer of [VA], methyl (20RS)-16 α ,17 α -butyridenedioxy-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate [VI], the 20R-epimer of [VI], methyl (20RS)-16 α ,17 α -butyridenedioxy-9 α -fluoro-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate [VII], the 20R-epimer of [VII], methyl (20RS)-16 α ,17 α -butyridenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate [VIII], the 20R-epimer of [VIII], methyl (22RS)-16 α ,17 α -butyridenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3,20-dioxo-pregna-1,4-diene-21-oate [IX] and the 22R-epimer of [IX] and

b) a pharmaceutical acceptable film forming water insoluble or water soluble polymer, or in case of a core consisting of a seed in which a glucocorticosteroid as defined above is homogeneously distributed, an optionally layer of a pharmaceutically acceptable film forming water insoluble polymer or a mixture of water insoluble polymers or a mixture of water soluble and water insoluble polymers and

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iii) a membrane surrounding said core and layer and containing a pharmaceutically acceptable film-forming anionic carboxylic polymer being soluble with difficulty at low pH but being soluble at a higher pH, either alone or in combination with a pharmaceutically acceptable film-forming water insoluble polymer,

the thickness of said layer or said membrane and/or the ratio of said anionic carboxylic polymer to said insoluble polymer being effective to prevent release of said glucocorticosteroid from said pellet in gastric fluids, but to permit release of said glucocorticosteroid from said pellet in intestinal fluids at a rate allowing treatment of the part of the intestinal tract where the disease resides, i.e. at a rate corresponding to a release time of 1 to 50 hours, preferably 5 to 10 hours when treating the small intestine and 25 to 50 hours when treating the large intestine, said rate being measured in vitro as a dissolution rate of said unit in simulated gastric and intestinal fluids, when measured in a flow through cell at 8 mL/min and 37° C. substantially corresponds to the following for units intended for treating the small intestine:

- a) not more than 10%, preferably not more than 5%, of the total glucocorticosteroid is released after two hours in simulated gastric fluid in said assembly,
 - b) from 15 to 55%, preferably from 20 to 50%, of the total glucocorticosteroid is released after two hours in simulated intestinal fluid in said assembly,
 - c) from 35 to 80%, preferably from 40 to 70%, of the total glucocorticosteroid is released after four hours in simulated intestinal fluid in said assembly,
 - d) not less than 60, preferably 60 to 90%, of the total glucocorticosteroid is released after eight hours in simulated intestinal fluid in said assembly,
 - e) not less than 80% of the total glucocorticosteroid is released after twelve hours in simulated intestinal fluid in said assembly,
- and for units intended for treating the large intestine:
- a) not more than 10%, preferably not more than 5%, of the total glucocorticosteroid is released after two hours in simulated gastric fluid in said assembly,
 - b) from 5 to 30%, preferably from 10 to 30%, of the total glucocorticosteroid is released after four hours in simulated intestinal fluid in said assembly,
 - c) from 20 to 65%, preferably from 35 to 55%, of the total glucocorticosteroid is released after twelve hours in simulated intestinal fluid in said assembly,
 - d) from 40 to 95%, preferably from 55 to 85%, of the total glucocorticosteroid is released after twenty-four hours in simulated intestinal fluid in said assembly,
 - e) not less than 70%, preferably not less than 80%, of the total glucocorticosteroid is released after forty-eight hours in simulated intestinal fluid in said assembly.

In one embodiment of the composition there is a layer which comprises budesonide or the 22R epimer thereof and a water soluble or water insoluble polymer beneath the membrane surrounding the pellet.

In another embodiment of the composition the polymeric material of the layer in which budesonide or its 22R epimer is embedded is selected from polyvinylpyrrolidone and hydroxypropylmethylcellulose or alternatively from ethylcellulose, cellulose acetate and copolymers of acrylic and methacrylic acid esters.

In still another embodiment of the composition the layer which comprises budesonide or its 22R epimer and a water soluble or water insoluble polymer includes one or more additional components selected from plasticizers, anti-adhesives and surfactants.

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WORKING EXAMPLES

The following pharmaceutical compositions can be used in the treatment of bowel diseases according to the invention.

EXAMPLE 1

	mg/capsule
Budesonide micronized	1.0
Sugar spheres	321
Aquacoat ECD 30	6.6
Acetyltributyl citrate	0.5
Polysorbate 80	0.1
Eudragit L100-55	17.5
Triethylcitrate	1.8
Talc	8.8
Antifoam MMS	0.01

Budesonide (32.2 g) was suspended in the Aquacoat ECD 30 dispersion (0.70 kg) with the aid of the Polysorbate 80 (0.42 g) together with acetyltributyl citrate (15.8 g). The mixture was sprayed on to sugar spheres (10.2 kg) in a fluid bed apparatus. The enteric coating consisting of the Eudragit L100-55 dispersion, (Eudragit L100-55 (0.558 kg), triethylcitrate (55.8 g), talc (0.279 kg), Antifoam MMS (0.44 g) and Polysorbate 80 (2.79 g)) was then sprayed on the spheres. The pellets were dried in the fluid bed apparatus, sieved and filled in hard gelatine capsules.

The finished pellets were then subjected to a dissolution test as follows:

Apparatus: Flow-through cells (Sotax Dissotest CE6, equipped with 12 mm cells) at a flow rate of 8 mL/min and at 37° C.

Medium: Simulated gastric fluid (SGF), pH 1.2 and simulated intestinal fluid (SIF), pH 7.5 according to USP without enzymes.

Method: For the dissolution test in simulated gastric fluid, 2.8 g of pellets, and for the test in simulated intestinal fluid, 1.4 g of pellets were placed in the cells and the test commenced. For specified time periods fractions were collected and analyzed for budesonide by a liquid chromatographic method. The percentage dissolution at each time point was calculated. The results are shown in Table 1.

TABLE 1

Dissolution of budesonide of Example 1						
Medium	Percentage dissolution after					
	1 hour	2 hours	4 hours	8 hours	12 hours	
SGF	1	2	3	—	—	
SIF	34	53	75	92	97	

EXAMPLE 2

	mg/capsule
Budesonide micronized	2.0
Sugar spheres	292
Aquacoat ECD 30	4.8
Acetyltributyl citrate	0.4

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	mg/capsule
Polysorbate 80	0.01
Eudragit NE30D	17.5
Eudragit S100	17.5
Talc	17.5

Budesonide (3.5 g) was suspended in the Aquacoat ECD 30 dispersion (28.0 g) with the aid of the Polysorbate 80 (0.02 g) together with acetyltributyl citrate (0.63 g). The mixture was sprayed on to sugar spheres (510 g) in a fluid bed apparatus. The rate-limiting and enteric coating consisting of Eudragit S100 (30.0 g) and talc (30.0 g) suspended in the Eudragit NE30D dispersion (100 g) with the aid of Polysorbate 80 (0.3 g) was then sprayed on the spheres. The pellets were dried, sieved and filled in hard gelatine capsules.

The finished pellets were then subjected to a dissolution test as follows:

Apparatus: Flow-through cells (Sotax Dissotest CE6, equipped with 12 mm cells) at a flow rate of 8 mL/min and at 37° C.

Medium: Simulated gastric fluid (SGF), pH 1.2 and simulated intestinal fluid (SIF), pH 7.5 according to USP without enzymes.

Method: For the dissolution test in simulated gastric fluid and simulated intestinal fluid, 2.8 g of pellets were placed in the cells and the test commenced. For specified time periods fractions were collected and analyzed for budesonide by a liquid chromatographic method. The percentage dissolution at each time point was calculated. The results are shown in Table 2.

TABLE 2

Dissolution of budesonide of Example 2									
Medium	Percentage dissolution after (hours)								
	1	2	4	8	12	18	24	36	48
SGF	0	0	1	—	—	—	—	—	—
SIF	5	8	13	20	27	35	43	56	67

EXAMPLE 3

	mg/capsule
Budesonide micronized	2.0
Sugar spheres	305
Aquacoat ECD 30	5.0
Acetyltributyl citrate	0.4
Polysorbate 80	0.14
Eudragit NE30D	12.6
Eudragit S100	12.6
Talc	12.6

Budesonide (6.69 g) was suspended in the Aquacoat ECD 30 dispersion (56.0 g) with the aid of the Polysorbate 80 (0.04 g) together with acetyltributyl citrate (1.26 g). The mixture was sprayed on to sugar spheres (1020 g) in a fluid bed apparatus. The rate-limiting and enteric coating consisting of Eudragit S100 (42.0 g) and talc (42.0 g) suspended in the Eudragit NE30D dispersion (140 g) with the aid of Polysorbate 80 (0.42 g) was then sprayed on the spheres. The pellets were dried, sieved and filled in hard gelatine capsules.

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The finished pellets were then subjected to a dissolution test as follows:

Apparatus: Flow-through cells (Sotax Dissotest CE6, equipped with 12 mm cells) at a flow rate of 8 mL/min and at 37° C.

Medium: Simulated gastric fluid (SGF), pH 1.2 and simulated intestinal fluid (SIF), pH 7.5 according to USP without enzymes.

Method: For the dissolution test in simulated gastric fluid, 2.8 g of pellets, and for the test in simulated intestinal fluid, 2.1 g of pellets were placed in the cells and the test commenced. For specified time periods fractions were collected and analyzed for budesonide by a liquid chromatographic method. The percentage dissolution at each time point was calculated. The results are shown in Table 3.

TABLE 3

Dissolution of budesonide of Example 3								
Medium	Percentage dissolution after (hours)							
	1	2	4	8	12	18	24	48
SGF	0	1	1	—	—	—	—	—
SIF	6	10	17	27	35	46	55	80

EXAMPLE 4

	mg/capsule
Budesonide micronized	0.5
Sugar spheres	286
Aquacoat ECD 30	24.2
Acetyltributyl citrate	1.8
Eudragit NE30D	12.6
Eudragit S100	12.6
Talc	12.6

Budesonide (0.90 g) was suspended in the Aquacoat ECD 30 dispersion (144 g) together with acetyltributyl citrate (1.82 g). The mixture was sprayed on to sugar spheres (510 g) in a fluid bed apparatus. The rate-limiting and enteric coating consisting of Eudragit S100 (22.5 g) and talc (22.5 g) suspended in the Eudragit NE30D dispersion (75.0 g) was then sprayed on the spheres. The pellets were dried, sieved and filled in hard gelatine capsules.

The finished pellets were then subjected to a dissolution test as follows:

Apparatus: Flow-through cells (Sotax Dissotest CE6, equipped with 12 mm cells) at a flow rate of 8 mL/min and at 37° C.

Medium: Simulated gastric fluid (SGF), pH 1.2 and simulated intestinal fluid (SIF), pH 7.5 according to USP without enzymes.

Method: For the dissolution test in simulated gastric fluid, 2.8 g of pellets, and for the test in simulated intestinal fluid, 2.1 g of pellets were placed in the cells and the test commenced. For specified time periods fractions were collected and analyzed for budesonide by a liquid chromatographic method. The percentage dissolution at each time point was calculated. The results are shown in Table 4.

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TABLE 4

Dissolution of budesonide of Example 4						
Medium	Percentage dissolution after (hours)					
	1	2	4	8	12	18
SGF	1	1	3	—	—	—
SIF	7	15	29	50	67	84

Absorption Data for the Budesonide Formulation Prepared in Example 1

Each of two healthy volunteers took the formulation in Example 1 corresponding to 9 mg of budesonide. Blood samples were drawn at different time-points up to 48 hours after drug administration. Plasma samples were analysed for budesonide by a specific HPLC-RIA method. The absorption process was estimated by the numerical point to point deconvolution method on plasma concentration data. The absorption values were scaled to the same final level by dividing the values with the absorption value at the last time-point when absorption was considered complete. The values are presented in Table 1A. The absolute bioavailability was 10.8% and 9.6% for the two subjects, respectively. For comparison, the absolute bioavailability of a fast releasing budesonide capsule is 10 to 15%, and the mean absorption time is less than 2 hours. Of the dose absorbed about 30% and 55% was absorbed in the time interval 2–12 hours in the two subjects, respectively. Absorption in this time interval probably occurs during the passage of the formulation through ileum, caecum and proximal colon.

TABLE 1A

Subj	Percentage absorption after (hours)						
no.	1	2	4	8	12	24	36
3	—	7	14	23	37	83	100
5	13	39	61	85	94	99	100

Absorption Data for the Budesonide Formulation Prepared in Example 2

Each of two healthy volunteers took the formulation in Example 2 corresponding to 20 mg of budesonide. Blood samples were drawn at different time-points up to 72 hours after drug administration. Plasma samples were analysed for budesonide by a specific HPLC-RIA method. The absorption process was estimated by the numerical point to point deconvolution method on plasma concentration data. The absorption values were scaled to the same final level by dividing the values with the absorption value at the last time-point when absorption was considered complete. The values are presented in Table 2A. The absolute bioavailability was 3.1% and 2.3% for the two subjects, respectively. For comparison, the absolute bioavailability of a fast releasing budesonide capsule is 10 to 15%, and the mean absorption time is less than 2 hours. Of the dose absorbed about 68% and 67% was absorbed in the time interval 6–36 hours in the two subjects, respectively. Absorption in this time interval probably occurs during the passage of the formulation through caecum and colon-rectum.

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TABLE 2A

Absorption of budesonide of Example 2											
Subj	Percentage absorption after (hours)										
no.	2	4	6	8	12	24	36	48	60	72	
4	5	15	24	29	48	80	92	96	98	100	
5	5	19	33	43	57	87	100				

Absorption Data for the Budesonide Formulation Prepared in Example 3

Each of two healthy volunteers took the formulation in Example 3 corresponding to 20 mg of budesonide. Blood samples were drawn at different time-points up to 72 hours after drug administration. Plasma samples were analysed for budesonide by a specific HPLC-RIA method. The absorption process was estimated by the numerical point to point deconvolution method on plasma concentration data. The absorption values were scaled to the same final level by dividing the values with the absorption value at the last time-point when absorption was considered complete. The values are presented in Table 3A. The absolute bioavailability was 6.3% and 4.9% for the two subjects, respectively. For comparison, the absolute bioavailability of a fast releasing budesonide capsule is 10 to 15%, and the mean absorption time is less than 2 hours. Of the dose absorbed about 67% and 71% was absorbed in the time interval 6–36 hours in the two subjects, respectively. Absorption in this time interval probably occurs during the passage of the formulation through caecum and colon-rectum.

TABLE 3A

Absorption of budesonide of Example 3											
Subj	Percentage absorption after (hours)										
no.	2	4	6	8	12	24	36	48	60	72	
1	6	16	27	35	53	83	94	98	99	100	
3	1	2	6	16	28	57	78	91	97	100	

Absorption Data for the Budesonide Formulation Prepared in Example 4

Each of two healthy volunteers took the formulation in Example 4 corresponding to 20 mg of budesonide. Blood samples were drawn at different time-points up to 72 hours after drug administration. Plasma samples were analysed for budesonide by a specific HPLC-RIA method. The absorption process was estimated by the numerical point to point deconvolution method on plasma concentration data. The absorption values were scaled to the same final level by dividing the values with the absorption value at the last time-point when absorption was considered complete. The values are presented in Table 4A. The absolute bioavailability was 16.2% and 3.4% for the two subjects, respectively. For comparison, the absolute bioavailability of a fast releasing budesonide capsule is 10 to 15%, and the mean absorption time is less than 2 hours. Of the dose absorbed about 71% and 44% was absorbed in the time interval 6–36 hours in the two subjects, respectively. Absorption in this time interval probably occurs during the passage of the formulation through caecum and colon-rectum.

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TABLE 4A

Absorption of budesonide of Example 4										
Subj	Percentage absorption after (hours)									
no.	2	4	6	8	12	24	36	48	60	72
1	3	16	24	36	56	86	94	98	99	100
2	8	33	51	62	72	89	95	97	99	100

What is claimed is:

1. A method for the prevention or treatment of a bowel disease selected from the group consisting of ulcerative colitis, Crohn's colitis in its active phase, Crohn's colitis in its chronic phase as relapse preventing therapy and Crohn's disease in the small intestine as relapse preventing therapy, which comprises the oral administration per 24-hour period of a controlled-release pharmaceutical formulation comprising 2–20 mg of a compound selected from budesonide and the 22-R epimer thereof and which will release the compound at the site of the disease to be treated, to a patient in need of such prevention or treatment.

2. A method according to claim 1, wherein the compound is budesonide.

3. A method according to claim 1, wherein the 2–20 mg of the compound administered in a 24-hour period are divided into 1 to 4 doses.

4. A method according to claim 3, wherein the compound is administered in a unit dose of from 0.25–20 mg.

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5. A method according to claim 4, wherein the compound is administered in a unit dose of from 2–5 mg.

6. A method according to claim 4, wherein the compound is administered in a unit dose of 0.5, 1.0 or 2.0 mg.

7. A method according to claim 1, wherein the compound is the 22-R epimer of budesonide.

8. A method according to any one of claims 1–6 and 7, wherein the disease is ulcerative colitis.

9. A method according to claim 8, wherein the formulation is in a form which will release the compound in the colon.

10. A method according to claim 8, wherein the formulation is in a form which will release the compound over a period of from 25–50 hours.

11. A method according to claim 8, wherein the formulation is in a form which will release the compound over a period of from 25–50 hours.

12. A method according to any one of claims 1 to 6 and 7, wherein the condition to be treated is Crohn's disease of the ileum and the formulation is in a form which will release the compound in the small intestine.

13. A method according to claim 12, wherein the formulation is in a form which will release the compound over a period of from 1–50 hours.

14. A method according to claim 13, wherein the formulation is in a form which will release the compound over a period of from 5–10 hours.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,423,340 B2
DATED : July 23, 2002
INVENTOR(S) : Ulmuis

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,

Item [30], **Foreign Application Priority Data,**

Filing date should be -- Nov. 22, 1989 --.

Column 1,

Line 5, delete "field" and substitute therefor -- filed --.

Column 2,

Line 55, delete "11 β ," and substitute therefor -- 11 β - --.

Lines 58-59, delete "11 β , 21-dihydroxypregn-" and substitute therefor
-- 11 β -hydroxypregn- --.

Column 5,

Line 31, insert "," after -- first --.

Line 44, delete "asterified" and substitute therefor -- esterified --.

Line 59, delete "polyethyleneglycols" and substitute therefor -- polyethylene glycols --.

Column 10,

Lines 62-63, delete "the test were placed in the cells and".

Column 14,

Line 15, "claim 8" should read -- claim 9 --.

Signed and Sealed this

Third Day of June, 2003

A handwritten signature in black ink, appearing to read "James E. Rogan", with a horizontal line drawn underneath it.

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

EXHIBIT B

US005643602A

United States Patent [19][11] **Patent Number:** **5,643,602****Ulmius**[45] **Date of Patent:** **Jul. 1, 1997****[54] ORAL COMPOSITION FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE**[75] Inventor: **Jan Ulmuis**, Lund, Sweden[73] Assignee: **Astra Aktiebolag**, Sodertalje, Sweden[21] Appl. No.: **240,078**[22] Filed: **May 9, 1994****Related U.S. Application Data**

[63] Continuation of Ser. No. 855,623, filed as PCT/SE90/00738, Nov. 15, 1990, abandoned.

[30] Foreign Application Priority Data

Nov. 22, 1989 [SE] Sweden 8903914

[51] Int. Cl.⁶ **A61K 9/58; A61K 9/62; A61K 9/14; A61K 47/32**[52] U.S. Cl. **424/462; 424/461; 424/494; 424/495; 424/497; 514/951; 514/925**[58] Field of Search **424/451, 461-62, 424/494-95, 497, 471-72; 514/915, 925-26****[56] References Cited****U.S. PATENT DOCUMENTS**

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[57]

ABSTRACT

An oral pharmaceutical composition is described for targeted slow release in the treatment of inflammatory bowel diseases. Also described are pharmaceutical compositions for peroral treatment targeted to different areas of the intestinal tract afflicted by ulcerative colitis and certain aspects of Crohn's disease.

26 Claims, No Drawings

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ORAL COMPOSITION FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

This application is a continuation of application Ser. No. 07/855,623, filed as PCT/SE90/00738 Nov. 15, 1990 now abandoned.

FIELD OF THE INVENTION

The present invention relates to oral pharmaceutical compositions for use in the treatment of inflammatory bowel diseases and the use of certain glucocorticosteroids in the preparation of pharmaceutical compositions for the treatment by the oral route of certain inflammatory bowel diseases.

BACKGROUND OF THE INVENTION

Inflammatory bowel disease is the term generally applied to two diseases, namely ulcerative colitis and Crohn's disease.

Ulcerative colitis is a chronic inflammatory disease of unknown aetiology afflicting only the large bowel and, except when very severe, limited to the bowel mucosa. The course of the disease may be continuous or relapsing, mild or severe. It is curable by total colectomy which may be needed for acute severe disease or chronic unremitting disease. Most patients with ulcerative colitis are managed medically rather than surgically.

Crohn's disease is also a chronic inflammatory disease of unknown aetiology but, unlike ulcerative colitis, it can affect any part of the bowel. Although lesions may start superficially, the inflammatory process extends through the bowel wall to the draining lymph nodes. As with ulcerative colitis, the course of the disease may be continuous or relapsing, mild or severe but, unlike ulcerative colitis it is not curable by resection of the involved segment of bowel. Most patients with Crohn's disease come to surgery at some time, but subsequent relapse is common and continuous medical treatment is usual.

For treatment of acute attacks of ulcerative colitis, glucocorticosteroids such as prednisone or prednisolone acetate are almost invariably used and given by mouth for the average acute attack or relapse, or locally, by enema.

After remission has been achieved, sulphasalazine is the maintenance treatment of choice in treating ulcerative colitis. This drug, however, has a significant number of side effects chiefly due to absorption of the sulphapyridine moiety from the colon. Recently compounds which contain only 5-aminosalicylic acid have been developed; these are as effective as sulphasalazine and do not have the sulphapyridine side effects but do have side effects of their own, notably diarrhoea.

Glucocorticosteroids are, however, not used for maintenance of remission in ulcerative colitis; doses that do not produce unacceptable side effects are ineffective, and patients who need chronic high dose glucocorticosteroids for control of their disease almost invariably are treated by colectomy.

As with ulcerative colitis, glucocorticosteroids are the treatment of choice for severe active Crohn's disease, but ideally only to achieve remission, after which they should be stopped. However, all too frequently the disease does not satisfactorily remit, and glucocorticosteroids may be necessary to maintain control of symptoms. Sulphasalazine is also useful in less severe cases, particularly for disease involving the colon.

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Very often in Crohn's disease, however, primary medical treatment of the disease process is ineffective, and only symptomatic treatment is of value i.e. analgesics for pain and opiates for diarrhoea. Most patients eventually require surgery.

DISCLOSURE OF THE INVENTION

Our studies indicate that the compositions according to the present invention may advantageously be used in the treatment of ulcerative colitis including idiopathic proctitis and certain aspects of Crohn's disease by the oral route.

In ulcerative colitis the compositions can be used for the treatment of both active and chronic continuous disease and as a relapse preventing treatment (i.e. maintenance therapy once remission has been achieved).

In Crohn's disease the compositions can be used for the treatment of Crohn's colitis in its active phase and as a relapse preventing therapy (i.e. maintenance therapy once remission has been achieved), and for the treatment of the small intestine as a relapse preventing treatment (i.e. maintenance therapy).

It has been found that the diseases defined above can be treated using the anti-inflammatory steroids

(22RS)-16 α ,17 α -butyridenedioxy-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione [I],

the 22R-epimer of [I],

(22RS)-16 α ,17 α -butyridenedioxy-9 α -fluoro-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione [II],

the 22R-epimer of [II],

(22RS)-16 α ,17 α -butyridenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione [III],

the 22R-epimer of [III],

(22RS)-21-acetoxy-16 α ,17 α -butyridenedioxy-11 β -hydroxy-pregna-1,4-diene-3,20-dione [IA],

the 22R-epimer of [IA],

(22RS)-21-acetoxy-16 α ,17 α -butyridenedioxy-9 α -fluoro-11 β -hydroxy-pregna-1,4-diene-3,20-dione [IIA],

the 22R-epimer of [IIA],

(22RS)-21-acetoxy-16 α ,17 α -butyridene-dioxy-6 α ,9 α -difluoro-11 β -hydroxy-1,4-diene-3,20-dione [IIIA],

the 22R-epimer of [IIIA],

(22RS)-16 α ,17 α -butyridenedioxy-11 β ,21-dihydroxy-pregna-4-ene-3,20-dione [IV],

the 22R-epimer of [IV],

(22RS)-16 α ,17 α -pentylidenedioxy-11 β ,21-dihydroxy-pregna-4-ene-3,20-dione [V],

the 22R-epimer of [V],

(22RS)-21-acetoxy-16 α ,17 α -butyridenedioxy-11 β ,hydroxypreg-4-ene-3,20-dione [IVA],

the 22R-epimer of [IVA],

(22RS)-21-acetoxy-16 α ,17 α -pentylidenedioxy-11 β ,hydroxypreg-4-ene-3,20-dione [VA],

the 22R-epimer of [VA],

methyl (20RS)-16 α ,17 α -butyridenedioxy-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate [VI],

the 20R-epimer of [VI],

methyl (20RS)-16 α ,17 α -butyridenedioxy-9 α -fluoro-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate [VII],

the 20R-epimer of [VII],

methyl (20RS)-16 α ,17 α -butyridenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate [VIII],

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the 20R-epimer of [VIII],
methyl (22RS)-16 α ,17 α -butylidenedioxy-6 α ,9 α -
difluoro-11 β -hydroxy-3,20-dioxopregna-1,4-diene-21-
oate [IX] and

the 22R-epimer of [IX].

Compound [I] has the approved name "budesonide".

Compound [I] and its 22R-epimer are particular preferred compounds.

Budesonide and compounds [II], [III], [IA], [IIA] and [IIIA] are described and claimed in Swedish Patent Specification 378 109. Budesonide is known to have an anti-inflammatory activity and, compared to prednisone, prednisolone and other glucocorticosteroids, an advantageous ratio between local and systemic effect when administered topically to the skin or to the lungs by inhalation.

Budesonide is a potent steroid, which is successfully used when locally treating (via aerosol) asthma and rhinitis. Also controlled trials of budesonide enema for locally treating proctitis and distal ulcerative colitis are in progress (Danielsson Å et al: A controlled randomized trial of budesonide versus prednisolone retention enemas in active distal ulcerative colitis, *Scand. J. Gastroenterol.* 22:987-992, 1987 and Danielsson Å et al: Controlled trial of budesonide enema and placebo in proctitis and distal ulcerative colitis. *Scand. J. Gastroenterol.* 24, supplement 159:88). The use of oral budesonide in the treatment of small bowel Crohn's disease in its active phase has been described (Wolman SL: Use of oral budesonide in a patient with small bowel Crohn's disease and previous pseudotumor cerebri secondary to steroids. *Scand. J. Gastroenterol.* 24, Supplement 158:146-147).

The characteristic profile of budesonide when used for the treatment of these diseases is a high anti-inflammatory effect at the place of application but a low degree of unwanted systemic glucocorticoid side effects. The low degree of systemic side effects of budesonide is a result of a high first pass liver metabolism transferring budesonide into substantially less active metabolites.

Especially the 22R-epimer of budesonide seems to be very promising in the treatment of inflammatory bowel diseases as hereinbefore defined when orally administered because, compared to budesonide it is more potent, is more rapidly metabolised by the liver and thus less available in the systemic circulation and thereby causing less unwanted systemic effects.

The 22R-epimers of compounds [I], [II], [III], [IA], [IIA] and [IIIA] are described and claimed in Swedish Patent Specification 378 110.

Compounds [IV], [V], [IVA], [VA] and the 22R-epimers thereof are described and claimed in European Patent Specification 54010.

Compounds [VI], [VII], [VIII] and the 20R-epimers thereof are described and claimed in European Patent Application 143 764.

Compound [IX] and the 22R-epimer thereof are described and claimed in European Patent Application 232 690.

We have surprisingly found that the above identified glucocorticosteroids administered by the convenient oral route are of great potential benefit in the treatment of inflammatory bowel diseases as hereinbefore defined.

The above mentioned compounds thus potentially represents a very significant advance over other glucocorticosteroids which exert their effects systemically and other drugs previously used for the management of Crohn's disease, particularly in avoiding the systemic side effects normally associated with glucocorticosteroid therapy. The high first pass liver metabolism of the drug renders possible its safe

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use in the maintenance therapy of the disease as well as achieving remission in the acute phase. Although Crohn's disease is not a very common condition, it is a chronic and often debilitating disorder that can benefit from a safer and more effective treatment.

In ulcerative colitis, the drug may help to reduce the number of patients having to undergo surgery and in addition, its lack of systemic effects makes it possible to use the drug for maintenance therapy once remission has been achieved.

The invention therefore provides pharmaceutical compositions comprising the glucocorticosteroids hereinbefore defined for use in the treatment by the oral route of bowel diseases as hereinbefore defined.

The invention also provides the use of the glucocorticosteroids as hereinbefore defined in the preparation of pharmaceutical compositions for the treatment by the oral route of bowel diseases as hereinbefore defined.

The invention further provides a method of treatment of bowel diseases as hereinbefore defined wherein an effective dose of a glucocorticosteroid as hereinbefore defined is administered by the oral route to a human or animal subject suffering from said bowel disease.

In order for the oral composition containing the glucocorticosteroids as hereinbefore defined to be applicable for the treatment of the bowel diseases as hereinbefore defined the composition must be adjusted to this particular purpose. The adjusted composition is a further aspect of the present invention, and it can be used generally when treating ulcerative colitis and Crohn's disease.

The transit time through the gastro-intestinal canal for different dosage forms are rather well known. When the dosage form has been emptied from the stomach the transit through the small intestine takes 3 to 5 hours. The residence time in the large intestine is considerably longer, 25 to 50 hours. Ideally, as long as the dosage form remains in the stomach no release should occur. If Crohn's disease in small intestine is going to be treated the release should continue during about 5 hours after the dosage form has left the stomach. If the large intestine is going to be treated the release should ideally start at caecum, and continue for up to 50 hours.

The present invention utilizes pharmaceutical formulation techniques to provide compositions of a glucocorticosteroid for treating the inflammatory diseases of the bowel as hereinbefore defined. The glucocorticosteroid must have a chance to reach the inflamed part of the bowel in sufficient concentration and for a sufficient long time to exert its local action, in the case of Crohn's disease the whole bowel or only the small intestine and in the case of ulcerative colitis the caecum (cecum), colon and the rectum.

A multiple unit composition in a capsule has been found suitable for fulfilling the above-mentioned demands. In ulcerative colitis, the composition should be formulated so that the glucocorticosteroid is released preferentially during the passage of the colon. In Crohn's disease in the ileum the composition should be formulated so that the glucocorticosteroid is released preferentially during the passage of the small intestine. This can be accomplished by enteric and/or slow release coating of the units containing the glucocorticosteroid. Such formulations of glucocorticosteroids are novel.

The dosage range for treatment of the bowel diseases as hereinbefore defined is suitably 2-20 mg divided into 1 to 4 doses during a 24-hour period.

DETAILED DESCRIPTION

The units will have a size between 0.3 and 5 mm, preferably a size between 0.5 and 2 mm. The units will be

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administered in hard gelatine capsules, the size of which will depend on the dose administered.

Each unit comprises a core, a first layer on the core and a second layer on the first layer.

The core consists of a non-pareil seed, preferably having a diameter between 0.2 and 1.0 mm, to which the glucocorticosteroid is applied or a seed in which the glucocorticosteroid is homogeneously distributed. The excipients used to prepare the seeds comprise one or more of pharmaceutically acceptable materials, e.g. sugar, starch, microcrystalline cellulose, waxes and polymeric binding agents.

The first layer on the non-pareil seeds comprises the glucocorticosteroid and a water-soluble or water-insoluble polymer which acts both as binder for the glucocorticosteroid and as a rate-limiting layer for release of the glucocorticosteroid. Such polymers may be selected from cellulose derivatives, acrylic polymers and copolymers, vinyl polymers and other high molecular polymer derivatives or synthetic polymers such as methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, ethylcellulose, cellulose acetate, polyvinyl pyrrolidone, polyvidone acetate, polyvinyl acetate, polymethacrylates and ethylene-vinyl acetate copolymer or a combination thereof. Preferred film-forming polymers are ethylcellulose or copolymers of acrylic and methacrylic acid esters (Eudragit NE, Eudragit RL, Eudragit RS) in aqueous dispersion form.

The first, optionally rate-limiting layer on the seeds with homogeneously distributed glucocorticosteroid comprises a water insoluble polymer or a mixture of water insoluble polymers or a mixture of water soluble and water insoluble polymers mentioned above.

The polymers in the second layer may be selected from the group of anionic carboxylic polymers suitable for pharmaceutical purposes and being soluble with difficulty at a low pH but being soluble at a higher pH, the pH limit for solubility being in the interval of pH 4 to pH 7.5, said group comprising cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate and acrylic acid polymers e.g. partly esterified methacrylic acid polymers such as Eudragit L, Eudragit L100-55 and Eudragit S. These polymers may be used alone or in combination with each other or in combination with water insoluble polymers mentioned before. Preferred polymers are the Eudragits in aqueous dispersion form. The anionic carboxylic polymer comprises 25 to 100 % of the total polymer content.

The coatings may optionally comprise other pharmaceutically acceptable materials which improve the properties of the film-forming polymers such as plasticizers, anti-adhesives, surfactants, and diffusion-accelerating or diffusion-retarding substances.

Suitable plasticizers comprise phthalic acid esters, triacetin, dibutylsebacate, monoglycerides, citric acid esters and polyethylene glycols. Preferred plasticizers are acetyl-tributyl citrate and triethyl citrate.

Suitable antiadhesives comprise talc and metal stearates.

The amount of the first coating applied on the units is normally in the range between 0.5% and 30% by weight, preferably between 1% and 15%. This amount includes in the relevant case the weight of the steroid as well. The amount of the second coating applied on the units is normally in the range between 1% and 50% by weight, preferably between 2% and 25%, calculated on the weight of the coated units. The remainder constitutes the weight of the seed.

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The preparation of the controlled release pellet formulation according to the present invention is characterized in that a non-pareil seed is enclosed in a layer of a glucocorticosteroid as hereinbefore defined and a water soluble or water insoluble polymer or a seed with homogeneously distributed glucocorticosteroid as hereinbefore defined is optionally enclosed in a layer of a water insoluble polymer or a mixture of water insoluble polymers or a mixture of water soluble or water insoluble polymers which in turn is enclosed in a membrane of a film-forming anionic carboxylic polymer or a mixture of a film-forming anionic carboxylic polymer and a water insoluble polymer which permits release of the glucocorticosteroid as hereinbefore defined in a manner set out below.

The controlled release pellet formulation according to this invention is thus characterized in that the pellet comprises

- i) a core consisting of a non-pareil seed or a seed in which a glucocorticosteroid as defined below is homogeneously distributed and
- ii) in case of a core consisting of a non-pareil seed, a layer of
 - a) a glucocorticosteroid selected from the group consisting of (22RS)-16 α ,17 α -butylidenedioxy-11 β ,21-dihydroxypregna-1,4-diene-3,20-dione [I], the 22R-epimer of [I], (22RS)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione [II], the 22R-epimer of [II], (22RS)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione [III], the 22R-epimer of [III], (22RS)-21-acetoxy-16 α ,17 α -butylidene-dioxy-11 β -hydroxypregna-1,4-diene-3,20-dione [IA], the 22R-epimer of [IA], (22RS)-21-acetoxy-16 α ,17 α -butylidene-dioxy-9 α -fluoro-11 β -hydroxy-pregna-1,4-diene-3,20-dione [IIA], the 22R-epimer of [IIA], (22RS)-21-acetoxy-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-1,4-diene-3,20-dione [IIIA], the 22R-epimer of [IIIA], (22RS)-16 α ,17 α -butylidenedioxy-11 β ,21-dihydroxypregn-4-ene-3,20-dione [IV], the 22R-epimer of [IV], (22RS)-16 α ,17 α -pentylidenedioxy-11 β ,21-dihydroxypregn-4-ene-3,20-dione [V], the 22R-epimer of [V], (22RS)-21-acetoxy-16 α ,17 α -butylidene-dioxy-11 β ,hydroxypregn-4-ene-3,20-dione [IVA], the 22R-epimer of [IVA], (22RS)-21-acetoxy-16 α ,17 α -pentylidene-dioxy-11 β ,hydroxypregn-4-ene-3,20-dione [VA], the 22R-epimer of [VA], methyl (20RS)-16 α ,17 α -butylidenedioxy-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate [VI], the 20R-epimer of [VI], methyl (20RS)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate [VII], the 20R-epimer of [VII], methyl (20RS)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate [VIII], the 22R-epimer of [VIII],

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methyl (22RS)-16 α ,17 α -butylenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3,20-dioxo-pregna-1,4-diene-21-oate [IX] and the 22R-epimer of [IX] and

- b) a pharmaceutical acceptable film forming water insoluble or water soluble polymer, or

in case of a core consisting of a seed in which a glucocorticosteroid as defined above is homogeneously distributed, an optionally layer of a pharmaceutically acceptable film forming water insoluble polymer or a mixture of water insoluble polymers or a mixture of water soluble and water insoluble polymers and

- iii) a membrane surrounding said core and layer and containing a pharmaceutically acceptable film-forming anionic carboxylic polymer being soluble with difficulty at low pH but being soluble at a higher pH, either alone or in combination with a pharmaceutically acceptable film-forming water insoluble polymer,

the thickness of said layer or said membrane and/or the ratio of said anionic carboxylic polymer to said insoluble polymer being effective to prevent release of said glucocorticosteroid from said pellet in gastric fluids, but to permit release of said glucocorticosteroid from said pellet in intestinal fluids at a rate allowing treatment of the part of the intestinal tract where the disease resides, i.e. at a rate corresponding to a release time of 1 to 50 hours, preferably 5 to 10 hours when treating the small intestine and 25 to 50 hours when treating the large intestine, said rate being measured in vitro as a dissolution rate of said unit in simulated gastric and intestinal fluids, when measured in a flow through cell at 8 mL/min and 37° C. substantially corresponds to the following for units intended for treating the small intestine:

- a) not more than 10%, preferably not more than 5%, of the total glucocorticosteroid is released after two hours in simulated gastric fluid in said assembly,
 - b) from 15 to 55%, preferably from 20 to 50%, of the total glucocorticosteroid is released after two hours in simulated intestinal fluid in said assembly,
 - c) from 35 to 80%, preferably from 40 to 70%, of the total glucocorticosteroid is released after four hours in simulated intestinal fluid in said assembly,
 - d) not less than 60, preferably 60 to 90%, of the total glucocorticosteroid is released after eight hours in simulated intestinal fluid in said assembly,
 - e) not less than 80% of the total glucocorticosteroid is released after twelve hours in simulated intestinal fluid in said assembly,
- and for units intended for treating the large intestine:
- a) not more than 10%, preferably not more than 5%, of the total glucocorticosteroid is released after two hours in simulated gastric fluid in said assembly,
 - b) from 5 to 30%, preferably from 10 to 30%, of the total glucocorticosteroid is released after four hours in simulated intestinal fluid in said assembly,
 - c) from 20 to 65%, preferably from 35 to 55%, of the total glucocorticosteroid is released after twelve hours in simulated intestinal fluid in said assembly,
 - d) from 40 to 95%, preferably from 55 to 85%, of the total glucocorticosteroid is released after twenty-four hours in simulated intestinal fluid in said assembly,
 - e) not less than 70%, preferably not less than 80%, of the total glucocorticosteroid is released after forty-eight hours in simulated intestinal fluid in said assembly.

In one embodiment of the composition there is a layer which comprises budesonide or the 22R epimer thereof and

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a water soluble or water insoluble polymer beneath the membrane surrounding the pellet.

In another embodiment of the composition the polymeric material of the layer in which budesonide or its 22R epimer is embedded is selected from polyvinylpyrrolidone and hydroxypropylmethylcellulose or alternatively from ethylcellulose, cellulose acetate and copolymers of acrylic and methacrylic acid esters.

In still another embodiment of the composition the layer which comprises budesonide or its 22R epimer and a water soluble or water insoluble polymer includes one or more additional components selected from plasticizers, anti-adhesives adhesives and surfactants.

WORKING EXAMPLES

The following pharmaceutical compositions can be used in the treatment of bowel diseases according to the invention.

Example 1

	mg/capsule
Budesonide micronized	1.0
Sugar spheres	321
Aquacoat ECD 30	6.6
Acetyltributyl citrate	0.5
Polysorbate 80	0.1
Eudragit L100-55	17.5
Triethylcitrate	1.8
Talc	8.8
Antifoam MMS	0.01

Budesonide (32.2 g) was suspended in the Aquacoat ECD 30 dispersion (0.70 kg) with the aid of the Polysorbate 80 (0.42 g) together with acetyltributyl citrate (15.8 g). The mixture was sprayed on to sugar spheres (10.2 kg) in a fluid bed apparatus. The enteric coating consisting of the Eudragit L100-55 dispersion, (Eudragit L100-55 (0.558 kg), triethylcitrate (55.8 g), talc (0.279 kg), Antifoam MMS (0.44 g) and Polysorbate 80 (2.79 g)) was then sprayed on the spheres. The pellets were dried in the fluid bed apparatus, sieved and filled in hard gelatine capsules.

The finished pellets were then subjected to a dissolution test as follows:

Apparatus: Flow-through cells (Sotax Dissotest CE6, equipped with 12 mm cells) at a flow rate of 8 mL/min and at 37° C.

Medium: Simulated gastric fluid (SGF), pH 1.2 and simulated intestinal fluid (SIF), pH 7.5 according to USP without enzymes.

Method: For the dissolution test in simulated gastric fluid, 2.8 g of pellets, and for the test in simulated intestinal fluid, 1.4 g of pellets were placed in the cells and the test commenced. For specified time periods fractions were collected and analyzed for budesonide by a liquid chromatographic method. The percentage dissolution at each time point was calculated. The results are shown in Table 1.

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TABLE 1

Dissolution of budesonide of Example 1					
Medium	Percentage dissolution after				
	1 hour	2 hours	4 hours	8 hours	12 hours
SGF	1	2	3	—	—
SIF	34	53	75	92	97

Example 2

	mg/capsule
Budesonide micronized	2.0
Sugar spheres	292
Aquacoat ECD 30	4.8
Acetyltributyl citrate	0.4
Polysorbate 80	0.01
Eudragit NE30D	17.5
Eudragit S100	17.5
Talc	17.5

Budesonide (3.5 g) was suspended in the Aquacoat ECD 30 dispersion (28.0 g) with the aid of the Polysorbate 80 (0.02 g) together with acetyltributyl citrate (0.63 g). The mixture was sprayed on to sugar spheres (510 g) in a fluid bed apparatus. The rate-limiting and enteric coating consisting of Eudragit S100 (30.0 g) and talc (30.0 g) suspended in the Eudragit NE30D dispersion (100 g) with the aid of Polysorbate 80 (0.3 g) was then sprayed on the spheres. The pellets were dried, sieved and filled in hard gelatine capsules.

The finished pellets were then subjected to a dissolution test as follows:

Apparatus: Flow-through cells (Sotax Dissotest CE6, equipped with 12 mm cells) at a flow rate of 8 mL/min and at 37° C.

Medium: Simulated gastric fluid (SGF), pH 1.2 and simulated intestinal fluid (SIF), pH 7.5 according to USP without enzymes.

Method: For the dissolution test in simulated gastric fluid and simulated intestinal fluid, 2.8 g of pellets were placed in the cells and the test commenced. For specified time periods fractions were collected and analyzed for budesonide by a liquid chromatographic method. The percentage dissolution at each time point was calculated. The results are shown in Table 2.

TABLE 2

Dissolution of budesonide of Example 2									
Medium	Percentage dissolution after (hours)								
	1	2	4	8	12	18	24	36	48
SGF	0	0	1	—	—	—	—	—	—
SIF	5	8	13	20	27	35	43	56	67

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Example 3

	mg/capsule
Budesonide micronized	2.0
Sugar spheres	305
Aquacoat ECD 30	5.0
Acetyltributyl citrate	0.4
Polysorbate 80	0.14
Eudragit NE30D	12.6
Eudragit S100	12.6
Talc	12.6

Budesonide (6.69 g) was suspended in the Aquacoat ECD 30 dispersion (56.0 g) with the aid of the Polysorbate 80 (0.04 g) together with acetyltributyl citrate (1.26 g). The mixture was sprayed on to sugar spheres (1020 g) in a fluid bed apparatus. The rate-limiting and enteric coating consisting of Eudragit S100 (42.0 g) and talc (42.0 g) suspended in the Eudragit NE30D dispersion (140 g) with the aid of Polysorbate 80 (0.42 g) was then sprayed on the spheres. The pellets were dried, sieved and filled in hard gelatine capsules.

The finished pellets were then subjected to a dissolution test as follows:

Apparatus: Flow-through cells (Sotax Dissotest CE6, equipped with 12 mm cells) at a flow rate of 8 mL/min and at 37° C.

Medium: Simulated gastric fluid (SGF), pH 1.2 and simulated intestinal fluid (SIF), pH 7.5 according to USP without enzymes.

Method: For the dissolution test in simulated gastric fluid, 2.8 g of pellets, and for the test in simulated intestinal fluid, 2.1 g of pellets were placed in the cells and the test commenced. For specified time periods fractions were collected and analyzed for budesonide by a liquid chromatographic method. The percentage dissolution at each time point was calculated. The results are shown in Table 3.

TABLE 3

Dissolution of budesonide of Example 3								
Medium	Percentage dissolution after (hours)							
	1	2	4	8	12	18	24	48
SGF	0	1	1	—	—	—	—	—
SIF	6	10	17	27	35	46	55	80

Example 4

	mg/capsule
Budesonide micronized	0.5
Sugar spheres	286
Aquacoat ECD 30	24.2
Acetyltributyl citrate	1.8
Eudragit NE30D	12.6
Eudragit S100	12.6
Talc	12.6

Budesonide (0.90 g) was suspended in the Aquacoat ECD 30 dispersion (144 g) together with acetyltributyl citrate (1.82 g). The mixture was sprayed on to sugar spheres (510 g) in a fluid bed apparatus. The rate-limiting and enteric

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coating consisting of Eudragit S100 (22.5 g) and talc (22.5 g) suspended in the Eudragit NE30D dispersion (75.0 g) was then sprayed on the spheres. The pellets were dried, sieved and filled in hard gelatine capsules.

The finished pellets were then subjected to a dissolution test as follows:

Apparatus: Flow-through cells (Sotax Dissotest CE6, equipped with 12 mm cells) at a flow rate of 8 mL/min and at 37° C.

Medium: Simulated gastric fluid (SGF), pH 1.2 and simulated intestinal fluid (SIF), pH 7.5 according to USP without enzymes.

Method: For the dissolution test in simulated gastric fluid, 2.8 g of pellets, and for the test in simulated intestinal fluid, 2.1 g of pellets were placed in the cells and the test commenced. For specified time periods fractions were collected and analyzed for budesonide by a liquid chromatographic method. The percentage dissolution at each time point was calculated. The results are shown in Table 4.

TABLE 4

Dissolution of budesonide of Example 4							
Medium	Percentage dissolution after (hours)						
	1	2	4	8	12	18	
SGF	1	1	3	—	—	—	
SIF	7	15	29	50	67	84	

Absorption data for the budesonide formulation prepared in Example 1

Each of two healthy volunteers took the formulation in Example 1 corresponding to 9 mg of budesonide. Blood samples were drawn at different time-points up to 48 hours after drug administration. Plasma samples were analysed for budesonide by a specific HPLC-RIA method. The absorption process was estimated by the numerical point to point deconvolution method on plasma concentration data. The absorption values were scaled to the same final level by dividing the values with the absorption value at the last time-point when absorption was considered complete. The values are presented in Table 1A. The absolute bioavailability was 10.8% and 9.6% for the two subjects, respectively. For comparison, the absolute bioavailability of a fast releasing budesonide capsule is 10 to 15%, and the mean absorption time is less than 2 hours. Of the dose absorbed about 30% and 55% was absorbed in the time interval 2–12 hours in the two subjects, respectively. Absorption in this time interval probably occurs during the passage of the formulation through ileum, caecum and proximal colon.

TABLE 1A

Absorption of budesonide of Example 1							
Subj no.	Percentage absorption after (hours)						
	1	2	4	8	12	24	36
3	—	7	14	23	37	83	100
5	13	39	61	85	94	99	100

Absorption data for the budesonide formulation prepared in Example 2

Each of two healthy volunteers took the formulation in Example 2 corresponding to 20 mg of budesonide. Blood

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samples were drawn at different time-points up to 72 hours after drug administration. Plasma samples were analysed for budesonide by a specific HPLC-RIA method. The absorption process was estimated by the numerical point to point deconvolution method on plasma concentration data. The absorption values were scaled to the same final level by dividing the values with the absorption value at the last time-point when absorption was considered complete. The values are presented in Table 2A. The absolute bioavailability was 3.1% and 2.3% for the two subjects, respectively. For comparison, the absolute bioavailability of a fast releasing budesonide capsule is 10 to 15%, and the mean absorption time is less than 2 hours. Of the dose absorbed about 68% and 67% was absorbed in the time interval 6–36 hours in the two subjects, respectively. Absorption in this time interval probably occurs during the passage of the formulation through caecum and colon-rectum.

TABLE 2A

Absorption of budesonide of Example 2											
Subj no.	Percentage absorption after (hours)										
	2	4	6	8	12	24	36	48	60	72	
4	5	15	24	29	48	80	92	96	98	100	
5	5	19	33	43	57	87	100				

Absorption data for the budesonide formulation prepared in Example 3

Each of two healthy volunteers took the formulation in Example 3 corresponding to 20 mg of budesonide. Blood samples were drawn at different time-points up to 72 hours after drug administration. Plasma samples were analysed for budesonide by a specific HPLC-RIA method. The absorption process was estimated by the numerical point to point deconvolution method on plasma concentration data. The absorption values were scaled to the same final level by dividing the values with the absorption value at the last time-point when absorption was considered complete. The values are presented in Table 3A. The absolute bioavailability was 6.3% and 4.9% for the two subjects, respectively. For comparison, the absolute bioavailability of a fast releasing budesonide capsule is 10 to 15%, and the mean absorption time is less than 2 hours. Of the dose absorbed about 67% and 71% was absorbed in the time interval 6–36 hours in the two subjects, respectively. Absorption in this time interval probably occurs during the passage of the formulation through caecum and colon-rectum.

TABLE 3A

Absorption of budesonide of Example 3											
Subj no.	Percentage absorption after (hours)										
	2	4	6	8	12	24	36	48	60	72	
1	6	16	27	35	53	83	94	98	99	100	
3	1	2	6	16	28	57	78	91	97	100	

Absorption data for the budesonide formulation prepared in Example 4

Each of two healthy volunteers took the formulation in Example 4 corresponding to 20 mg of budesonide. Blood samples were drawn at different time-points up to 72 hours after drug administration. Plasma samples were analysed for budesonide by a specific HPLC-RIA method. The absorption process was estimated by the numerical point to point

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deconvolution method on plasma concentration data. The absorption values were scaled to the same final level by dividing the values with the absorption value at the last time-point when absorption was considered complete. The values are presented in Table 4A. The absolute bioavailability was 16.2% and 3.4% for the two subjects, respectively. For comparison, the absolute bioavailability of a fast releasing budesonide capsule is 10 to 15%, and the mean absorption time is less than 2 hours. Of the dose absorbed about 71% and 44% was absorbed in the time interval 6–36 hours in the two subjects, respectively. Absorption in this time interval probably occurs during the passage of the formulation through caecum and colon-rectum.

TABLE 4A

Absorption of budesonide of Example 4											
Subj	Percentage absorption after (hours)										
no.	2	4	6	8	12	24	36	48	60	72	
1	3	16	24	36	56	86	94	98	99	100	
2	8	33	51	62	72	89	95	97	99	100	

I claim:

1. A controlled release pellet formulation for oral administration in the treatment of inflammatory bowel diseases wherein the pellet, having a size between 0.3 mm and 5 mm diameter, comprises

(i)

- a) a core consisting of a non-pareil seed or
- b) a seed in which a glucocorticosteroid as defined in this claim is homogeneously distributed; and

(ii)

- a) in the case of the core consisting of a non-pareil seed, a layer surrounding said core of
 - i) a glucocorticosteroid selected from the group consisting of (22R,S)-16 α ,17 α -butyridenedioxy-11 β ,21-dihydroxypregna-1,4-diene-3,20-dione (I); the 22R-epimer of (I); (22R,S)-16 α ,17 α -butyridenedioxy-9 α -fluoro-11 β ,21-dihydroxypregna-1,4-diene-3,20-dione (II); the 22R-epimer of (II); (22R,S)-16 α ,17 α -butyridenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxypregna-1,4-diene-3,20-dione (III); the 22R-epimer of (III); (22R,S)-21-acetoxy-16 α ,17 α -butyridenedioxy-11 β -hydroxypregna-1,4-diene-3,20-dione (IA); the 22R-epimer of (IA); (22R, S)-21-acetoxy-16 α -17 α -butyridenedioxy-9 α -fluoro-11 β -hydroxypregna-1,4-diene-3,20-dione (IIA); the 22R-epimer of (IIA); (22R, S)-21-acetoxy-16 α ,17 α -butyridenedioxy-6 α ,9 α -difluoro-11 β -hydroxypregna-1,4-diene-3,20-dione (IIIA); the 22R-epimer of (IIIA); (22R,S)-16 α ,17 α -butyridenedioxy-11 β ,21-dihydroxypregna-4-ene-3,20-dione (IV); the 22R-epimer of (IV); (22R,S)-16 α ,17 α -pentyridenedioxy-11 β ,21-dihydroxypregna-4-ene-3,20-dione (V); the 22R-epimer of (V); (22R, S)-21-acetoxy-16 α ,17 α -butyridenedioxy-11 β hydroxypregna-4-ene-3,20-dione (IVA); the 22R-epimer of (IVA); (22R,S)-21-acetoxy-16 α ,17 α -pentyridenedioxy-11 β hydroxypregna-4-ene-3,20-dione (VA); the 22R-epimer of (VA); methyl (20R,S)-16 α ,17 α -butyridenedioxy-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate (VI); the 20R-epimer of (VI); methyl (20R, S)-16 α ,17 α -

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butyridenedioxy-9 α -fluoro-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate (VII); the 20R-epimer of (VII); methyl (20R,S)-16 α ,17 α -butyridenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate (VIII); the 20R-epimer of (VIII); methyl (22R,S)-16 α ,17 β -butyridenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3,20-dioxo-pregna-1,4-diene-21-oate (IX) and the 22R-epimer of (IX), and

ii) a pharmaceutically acceptable film-forming, water-insoluble or water-soluble polymer, the layer comprising about 0.5–30% of the pellet by weight, or

b) in the case of the core consisting of a seed in which a glucocorticosteroid as defined in this claim is homogeneously distributed, a layer surrounding said core of a pharmaceutically acceptable, film-forming, water-insoluble polymer or a pharmaceutically acceptable mixture of film-forming, water-insoluble polymers, or a pharmaceutically acceptable mixture of film-forming, water-soluble and film-forming, water-insoluble polymers; and

(iii) a membrane surrounding both said core and said surrounding layer and containing a pharmaceutically acceptable, film-forming, anionic carboxylic polymer being difficult to dissolve at a low pH but being soluble at a higher pH of about 4 to 7.5, the polymer being either alone or in combination with a pharmaceutically acceptable, film-forming, water-insoluble polymer, the membrane comprising about 1–50% of the pellet by weight, the thickness of said layer or said membrane, or the ratio of said anionic carboxylic polymer to said water-insoluble polymer being effective to prevent release of said glucocorticosteroid from said pellet in gastric fluids, but to permit release of said glucocorticosteroid from said pellet in intestinal fluids at a rate allowing treatment of the part of the intestinal tract where the disease resides, which rate corresponds to a release time in vivo of 1 to 50 hours.

2. A controlled release pellet formulation for oral administration in the treatment of inflammatory bowel diseases wherein the pellet, having a size between 0.3 mm and 5 mm diameter, comprises

(i)

- a) a core consisting of a non-pareil seed or
- b) a seed in which a glucocorticosteroid as defined in this claim is homogeneously distributed; and

(ii)

- a) in case of the core consisting of a non-pareil seed, a layer surrounding said core of
 - i) a glucocorticosteroid selected from the group consisting of (22R,S)-16 α ,17 α -butyridenedioxy-11 β ,21-dihydroxypregna-1,4-diene-3,20-dione (I); the 22R-epimer of (I); (22R,S)-16 α ,17 α -butyridenedioxy-9 α -fluoro-11 β ,21-dihydroxypregna-4,1-diene-3,20-dione (II); the 22R-epimer of (II); (22R,S)-16 α ,17 α -butyridenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxypregna-1,4-diene-3,20-dione (III); the 22R-epimer of (III); (22R, S)-21-acetoxy-16 α ,17 α -butyridenedioxy-11 β -hydroxypregna-1,4-diene-3,20-dione (IA); the 22R-epimer of (IA); (22R,S)-21-acetoxy-16 α ,17 α -butyridenedioxy-9 α -fluoro-11 β -hydroxypregna-1,4-diene-3,20-dione (IIA); the 22R-epimer of (IIA); (22R,S)-21-acetoxy-16 α ,17 α -

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- hydroxypregna-1,4-diene-3,20-dione (IIIA); the 22R-epimer of (IIIA); (22R,S)-16 α ,17 α -butylidenedioxy-11 β ,21-dihydroxypregna-4-ene-3,20-dione (IV); the 22R-epimer of (IV); (22R,S)-16 α ,17 α -pentylidenedioxy-11 β ,21-dihydroxypregna-4-ene-3,20-dione (V); the 22R-epimer of (V); (22R,S)-21-acetoxy-16 α ,17 α -butylidenedioxy-11 β hydroxypregna-4-ene-3,20-dione (IVA); the 22R-epimer of (IVA); (22R,S)-21-acetoxy-16 α ,17 α -pentylidenedioxy-11 β hydroxypregna-4-ene-3,20-dione (VA); the 22R-epimer of (VA); methyl (20R,S)-16 α ,17 α -butylidenedioxy-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate (VI); the 20R-epimer of (VI); methyl (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate (VII); the 20R-epimer of (VII); methyl (20R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate (VIII); the 20R-epimer of (VIII); methyl (22R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3,20-dioxo-pregna-1,4-diene-21-oate (IX) and the 22R-epimer of (IX), and
- ii) ' a pharmaceutically acceptable, film-forming, water-insoluble or water-soluble polymer, the layer comprising about 0.5–30% of the pellet by weight, or
- (b) in the case of the core consisting of a seed in which a glucocorticosteroid as defined in this claim is homogeneously distributed, a layer surrounding said core of a pharmaceutically acceptable, film-forming, water-insoluble polymer, or a pharmaceutically acceptable mixture of film-forming, water-insoluble polymers, or a pharmaceutically acceptable mixture of film-forming, water-soluble and film-forming, water-insoluble polymers; and
- (iii) a membrane surrounding both said core and said surrounding layer and containing a pharmaceutically acceptable, film-forming, anionic carboxylic polymer being difficult to dissolve at a low pH but being soluble at a higher pH of about 4 to 7.5 the polymer being either alone or in combination with a pharmaceutically acceptable, film-forming, water-insoluble polymer, the membrane comprising about 1–50% of the pellet by weight, the thickness of said layer or said membrane, or the ratio of said anionic carboxylic polymer to said water-insoluble polymer being effective to prevent release of said glucocorticosteroid from said pellet in gastric fluids, but to permit release of said glucocorticosteroid from said pellet in intestinal fluids at a rate allowing treatment of the part of the intestinal tract where the disease resides, which rate corresponds to a release time in vivo of 1 to 50 hours, said rate being measured in vitro as a dissolution rate of a dosage unit in simulated gastric and intestinal fluids, when measured in a flow-through cell at 8 ml/min and 37° C. and corresponds to a formulation for treating the small intestine wherein:
- a) not more than 10% of the total glucocorticosteroid is released after two hours in simulated gastric fluid in said assembly,
- b) from 15 to 55% of the total glucocorticosteroid is released after two hours in simulated intestinal fluid in said assembly,
- c) from 35 to 80% of the total glucocorticosteroid is released after four hours in simulated intestinal fluid in said assembly,

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- d) not less than 60% of the total glucocorticosteroid is released after eight hours in simulated intestinal fluid in said assembly,
- e) not less than 80% of the total glucocorticosteroid is released after twelve hours in simulated intestinal fluid in said assembly,
- and a formulation for treating the large intestine wherein:
- f) not more than 10% of the total glucocorticosteroid is released after two hours in simulated gastric fluid in said assembly,
- g) from 5 to 30% of the total glucocorticosteroid is released after four hours in simulated intestinal fluid in said assembly,
- h) from 20 to 65% of the total glucocorticosteroid is released after twelve hours in simulated intestinal fluid in said assembly,
- i) from 40 to 95% of the total glucocorticosteroid is released after twenty-four hours in simulated intestinal fluid in said assembly, and
- j) not less than 70% of the total glucocorticosteroid is released after forty-eight hours in simulated intestinal fluid in said assembly.
3. A controlled release pellet formulation for oral administration in the treatment of inflammatory bowel diseases wherein the pellet, having a size between 0.3 mm and 5 mm in diameter, comprises
- (i)
- a) a core consisting of a non-pareil seed or
- b) a seed in which a glucocorticosteroid is homogeneously distributed; and
- (ii)
- a) in the case of the core consisting of a non-pareil seed, a layer surrounding said core of
- (i)' a glucocorticosteroid selected from the group consisting of (22R,S)-16 α ,17 α -butylidenedioxy-11 β ,21-dihydroxypregna-1,4-diene-3,20-dione (I); the 22R-epimer of (I); (22R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β ,21-dihydroxypregna-1,4-diene-3,20-dione (II); the 22R-epimer of (II); (22R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione (III); the 22R-epimer of (III); (22R,S)-21-acetoxy-16 α ,17 α -butylidenedioxy-11 β -hydroxypregna-1,4-diene-3,20-dione (IA); the 22R-epimer of (IA); (22R,S)-21-acetoxy-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxypregna-1,4-diene-3,20-dione (IIA); the 22R-epimer of (IIA); (22R,S)-21-acetoxy-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxypregna-1,4-diene-3,20-dione (IIIA); the 22R-epimer of (IIIA); (22R,S)-16 α ,17 α -butylidenedioxy-11 β ,21-dihydroxypregna-4-ene-3,20-dione (IV); the 22R-epimer of (IV); (22R,S)-16 α ,17 α -pentylidenedioxy-11 β ,21-dihydroxypregna-4-ene-3,20-dione (V); the 22R-epimer of (V); (22R,S)-21-acetoxy-16 α ,17 α -butylidenedioxy-11 β hydroxypregna-4-ene-3,20-dione (IVA); the 22R-epimer of (IVA); (22R,S)-21-acetoxy-16 α ,17 α -pentylidenedioxy-11 β hydroxypregna-4-ene-3,20-dione (VA); the 22R-epimer of (VA); methyl (20R,S)-16 α ,17 α -butylidenedioxy-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate (VI); the 20R-epimer of (VI); methyl (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate (VII);

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- the 20R-epimer of (VII); methyl (20R, S)-16 α , 17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-androsta-1,4-diene-3-one-17 β -carboxylate (VIII); the 20R-epimer of (VIII); methyl (22R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3,20-dioxo-pregna-1,4-diene-21-oate (IX) and the 22R-epimer of (IX), and
- (ii) a pharmaceutical acceptable, film-forming, water-insoluble or water-soluble polymer, the layer comprising about 0.5–30% of the pellet by weight, or
- (b) in the case of the core consisting of a seed in which a glucocorticosteroid as defined in this claim is homogeneously distributed, a layer surrounding said core of a pharmaceutically acceptable, film-forming, water-insoluble polymer, or a pharmaceutically acceptable mixture of film-forming, water-insoluble polymers or a pharmaceutically acceptable mixture of film-forming, water-soluble and film-forming, water-insoluble polymers; and
- (iii) a membrane surrounding both said core and said surrounding layer and containing a pharmaceutically acceptable, film-forming, anionic carboxylic polymer being difficult to dissolve at a low pH but being soluble at a higher pH of about 4 to 7.5, either alone or in combination with a pharmaceutically acceptable, film-forming, water insoluble polymer, the thickness of said layer or said membrane or the ratio of said anionic carboxylic polymer to said water-insoluble polymer being effective to prevent release of said glucocorticosteroid from said pellet in gastric fluids, but to permit release of said glucocorticosteroid from said pellet in intestinal fluids at a rate allowing treatment of the part of the intestinal tract where the disease resides, which rate corresponds to a release time in vivo of 1 to 50 hours said rate being measured in vitro as a dissolution rate of a dosage unit in simulated gastric and intestinal fluids, when measured in a flow through cell at 8 mL/min and 37° C., and corresponds to the following formulation for treating the small intestine, wherein:
- a) not more than 5% of the total glucocorticosteroid is released after two hours in simulated gastric fluid in said assembly,
 - b) from 20 to 50% of the total glucocorticosteroid is released after two hours in simulated intestinal fluid in said assembly,
 - c) from 40 to 70% of the total glucocorticosteroid is released after four hours in simulated intestinal fluid in said assembly,
 - d) 60% to 90% of the total glucocorticosteroid is released after eight hours in simulated intestinal fluid in said assembly,
 - e) not less than 80% of the total glucocorticosteroid is released after twelve hours in simulated intestinal fluid in said assembly,
- and a formulation for treating the large intestine, wherein
- f) not more than 5% of the total glucocorticosteroid is released after two hours in simulated gastric fluid in said assembly,
 - g) from 10 to 30% of the total glucocorticosteroid is released after four hours in simulated intestinal fluid in said assembly,
 - h) from 35 to 55% of the total glucocorticosteroid is released after twelve hours in simulated intestinal fluid in said assembly,

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- i) from 55 to 85% of the total glucocorticosteroid is released after twenty-four hours in simulated intestinal fluid in said assembly, and
 - j) not less than 80% of the total glucocorticosteroid is released after forty-eight hours in simulated intestinal fluid in said assembly.
4. The formulation according to claim 1 2 or 3 wherein the anionic carboxylic polymer ranges from 25% to 100% by weight of the total polymer content of said membrane.
5. The formulation according to claim 1, 2 or 3 wherein the anionic carboxylic polymer is selected from the group consisting of cellulose acetate phthalate, cellulose acetate trimellitate, polyvinyl acetate phthalate, hydroxypropyl-methylcellulose phthalate and methacrylic acid copolymer.
6. The formulation according to claim 1, 2 or 3 wherein the water insoluble polymer is selected from the group consisting of ethyl-cellulose, cellulose acetate, polyvinyl acetate, ethylene-vinyl acetate copolymer, amino methacrylate copolymers and polymethacrylic acid esters.
7. The formulation according to claim 1, 2 or 3 wherein the membrane includes one additional component selected from the group consisting of a plasticizer, an antiadhesive, a surfactant and a mixture thereof.
8. The formulation according to claim 1, 2 or 3 wherein the membrane ranges between 1 and 50% of the total weight of the pellet.
9. The formulation according to claim 1 2 or 3 wherein the glucocorticosteroid is budesonide or the 22R epimer thereof.
10. A formulation according to claim 1, 2 or 3, wherein the layer surrounding the core and beneath the membrane comprises budesonide or the 22R epimer thereof and a water-soluble or water insoluble film-forming polymer.
11. A formulation according to claim 10 wherein the layer includes one additional component selected from the group consisting of plasticizer, an antiadhesive, a surfactant and a mixture thereof.
12. The formulation according to claim 1, 2 or 3, wherein the layer beneath the membrane comprises a film-forming, water-insoluble polymer, a mixture of film-forming, water-insoluble polymers, or a mixture of water-insoluble and water-soluble, film-forming polymers.
13. A formulation according to claim 1, 2 or 3 wherein the polymeric material in which budesonide or the 22R epimer thereof is embedded is selected from the group consisting of polyvidone acetate, methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropylmethylcellulose, ethylcellulose, cellulose acetate, polyvinyl acetate, ethylene-vinylacetate copolymer, an amino methacrylate copolymer and a polymethacrylic acid ester.
14. A formulation according to claim 12 wherein the layer includes one additional component selected from the group consisting of a plasticizer, an antiadhesive, a surfactant and a mixture thereof.
15. The formulation according to claim 12 wherein the polymeric material is selected from the group consisting of polyvidone acetate, methylcellulose, hydroxypropylcellulose, ethylcellulose, cellulose acetate, polyvinyl acetate, ethylene vinylacetate copolymer, an amino methacrylate copolymer and a polymethacrylic acid ester.
16. The formulation according to claim 1, 2 or 3 wherein said core comprises budesonide or the 22R epimer thereof homogeneously distributed in pharmaceutically acceptable excipients or budesonide or the 22R epimer thereof in a layer on a non-pareil seed wherein the seed has a diameter between 0.2 and 1.5 mm.

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17. The formulation according to claim 1, 2 or 3 wherein the release time in vivo is 5 to 10 hours for treating the small intestine or 25 to 50 hours for treating the large intestine.

18. The formulation according to claim 2 wherein the in vitro dissolution rate of the dosage unit for treating the small intestine is not more than 5% of the total glucocorticosteroid released after two hours in the simulated gastric fluid; from 20% to 50% thereof released after two hours in the simulated intestinal fluid; from 40% to 70% thereof released after four hours in simulated intestinal fluid; from 60% to 90% thereof released after eight hours in simulated intestinal fluid and not less than 80% thereof released after twelve hours in simulated intestinal fluid.

19. The formulation according to claim 2 wherein the dissolution rate for a dosage unit intended for treating the large intestine is not more than 5% of the total glucocorticosteroid being released after two hours in simulated gastric fluid; from 10% to 30% thereof is released after four hours in simulated intestinal fluid; from 35% to 65 % thereof is released after twelve hours in simulated intestinal fluid; 55% to 85% thereof is released after twenty-four hours in simulated intestinal fluid; and not less than 80% thereof is released after forty-eight hours in simulated intestinal fluid.

20. The formulation of claim 1, 2 or 3 wherein the pellet is substantially free of precipitating electrolyte salts or cross-linking additives.

21. The formulation according to claim 1, 2 or 3, wherein the layer comprises between 1% and 15% (w/w) of the total weight of the coated pellet.

22. A pharmaceutical composition comprising the formulation according to claim 1, 2 or 3, useful for the treatment

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by the oral route of a bowel disease selected from the group consisting of ulcerative colitis, Crohn's colitis in its active phase, Crohn's colitis in its chronic phase as relapse-preventing therapy and Crohn's disease in the small intestines as a relapse preventing treatment.

23. A pharmaceutical composition as claimed in claim 22 wherein the bowel disease is ulcerative colitis.

24. The pharmaceutical composition as claimed in claim 22 wherein the glucocorticosteroid is budesonide or the 22R epimer thereof.

25. A capsule comprising a formulation of pellets according to claim 1, 2 or 3.

26. A process for the production of a pellet formulation according to any one of claims 1, 2 or 3 which comprises

a) making a core of pharmaceutically acceptable excipients with the glucocorticosteroid homogeneously distributed therein and optionally enclosing the core with a water-insoluble polymer, or a mixture of water-insoluble polymers or a mixture of water-soluble and water-insoluble polymers, or

b) enclosing a core of a non-pareil seed in a layer of a glucocorticosteroid and a water-soluble or water-insoluble polymer, and thereafter enclosing the coated core with a membrane of a film-forming, anionic carboxylic polymer, or a mixture of a film-forming, anionic carboxylic polymer and a water-insoluble polymer which permits release of the glucocorticosteroid in a manner set out in claim 1, 2 or 3.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,643,602
DATED : July 1, 1997
INVENTOR(S) : Ulmius

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 1 at column 14, line 7: "16~~α~~, 17^β" should be "16~~α~~, 17~~α~~".

Claim 2 at column 14, line 57: "pregna-4,1-diene-" should be "pregna-1,4-diene-".

Claim 4 at column 18, line 7: "12 or 3" should be "1, 2 or 3".

Claim 9 at column 18, line 27: "12 or 3" should be "1, 2 or 3".

Claim 11 at column 18, line 35: insert -- a -- before "plasticizer".

Claim 15 at column 18, line 57: "methylcellulonse" should be "methylcellulose".

Signed and Sealed this

First Day of June, 1999

Attest:



Q. TODD DICKINSON

Attesting Officer

Acting Commissioner of Patents and Trademarks

JS 44 (Rev. 11/04)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS ASTRAZENECA LP, AKTIEBOLAGET DRACO, KBI INC. and KBI-E INC. (b) County of Residence of First Listed Plaintiff _____ (EXCEPT IN U.S. PLAINTIFF CASES) (c) Attorney's (Firm Name, Address, and Telephone Number) Jack B. Blumenfeld, MORRIS, NICHOLS, ARSHT & TUNNELL LLP, 1201 North Market Street, P.O. Box 1347, Wilmington, DE 19899-1347, (302) 658-9200	DEFENDANTS BARR LABORATORIES, INC. and BARR PHARMACEUTICALS, INC. County of Residence of First Listed Defendant _____ (IN U.S. PLAINTIFF CASES ONLY) NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED. Attorneys (If Known) _____
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II. BASIS OF JURISDICTION (Place an "X" in One Box Only) <input type="checkbox"/> 1 U.S. Government Plaintiff <input type="checkbox"/> 2 U.S. Government Defendant <input checked="" type="checkbox"/> 3 Federal Question (U.S. Government Not a Party) <input type="checkbox"/> 4 Diversity (Indicate Citizenship of Parties in Item III)	III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant) (For Diversity Cases Only) <table style="width: 100%;"> <tr> <td style="width: 33%;">Citizen of This State</td> <td style="width: 10%;">PTF <input type="checkbox"/> 1</td> <td style="width: 10%;">DEF <input type="checkbox"/> 1</td> <td style="width: 33%;">Incorporated or Principal Place of Business In This State</td> <td style="width: 10%;">PTF <input type="checkbox"/> 4</td> <td style="width: 10%;">DEF <input type="checkbox"/> 4</td> </tr> <tr> <td>Citizen of Another State</td> <td>PTF <input type="checkbox"/> 2</td> <td>DEF <input type="checkbox"/> 2</td> <td>Incorporated and Principal Place of Business In Another State</td> <td>PTF <input type="checkbox"/> 5</td> <td>DEF <input type="checkbox"/> 5</td> </tr> <tr> <td>Citizen or Subject of a Foreign Country</td> <td>PTF <input type="checkbox"/> 3</td> <td>DEF <input type="checkbox"/> 3</td> <td>Foreign Nation</td> <td>PTF <input type="checkbox"/> 6</td> <td>DEF <input type="checkbox"/> 6</td> </tr> </table>	Citizen of This State	PTF <input type="checkbox"/> 1	DEF <input type="checkbox"/> 1	Incorporated or Principal Place of Business In This State	PTF <input type="checkbox"/> 4	DEF <input type="checkbox"/> 4	Citizen of Another State	PTF <input type="checkbox"/> 2	DEF <input type="checkbox"/> 2	Incorporated and Principal Place of Business In Another State	PTF <input type="checkbox"/> 5	DEF <input type="checkbox"/> 5	Citizen or Subject of a Foreign Country	PTF <input type="checkbox"/> 3	DEF <input type="checkbox"/> 3	Foreign Nation	PTF <input type="checkbox"/> 6	DEF <input type="checkbox"/> 6
Citizen of This State	PTF <input type="checkbox"/> 1	DEF <input type="checkbox"/> 1	Incorporated or Principal Place of Business In This State	PTF <input type="checkbox"/> 4	DEF <input type="checkbox"/> 4														
Citizen of Another State	PTF <input type="checkbox"/> 2	DEF <input type="checkbox"/> 2	Incorporated and Principal Place of Business In Another State	PTF <input type="checkbox"/> 5	DEF <input type="checkbox"/> 5														
Citizen or Subject of a Foreign Country	PTF <input type="checkbox"/> 3	DEF <input type="checkbox"/> 3	Foreign Nation	PTF <input type="checkbox"/> 6	DEF <input type="checkbox"/> 6														

IV. NATURE OF SUIT (Place an "X" in One Box Only)					
CONTRACT	TORTS	FORFEITURE/PENALTY	BANKRUPTCY	OTHER STATUTES	
<input type="checkbox"/> 110 Insurance <input type="checkbox"/> 120 Marine <input type="checkbox"/> 130 Miller Act <input type="checkbox"/> 140 Negotiable Instrument <input type="checkbox"/> 150 Recovery of Overpayment & Enforcement of Judgment <input type="checkbox"/> 151 Medicare Act <input type="checkbox"/> 152 Recovery of Defaulted Student Loans (Excl. Veterans) <input type="checkbox"/> 153 Recovery of Overpayment of Veteran's Benefits <input type="checkbox"/> 160 Stockholders' Suits <input type="checkbox"/> 190 Other Contract <input type="checkbox"/> 195 Contract Product Liability <input type="checkbox"/> 196 Franchise	PERSONAL INJURY <input type="checkbox"/> 310 Airplane <input type="checkbox"/> 315 Airplane Product Liability <input type="checkbox"/> 320 Assault, Libel & Slander <input type="checkbox"/> 330 Federal Employers' Liability <input type="checkbox"/> 340 Marine <input type="checkbox"/> 345 Marine Product Liability <input type="checkbox"/> 350 Motor Vehicle <input type="checkbox"/> 355 Motor Vehicle Product Liability <input type="checkbox"/> 360 Other Personal Injury PERSONAL INJURY <input type="checkbox"/> 362 Personal Injury - Med. Malpractice <input type="checkbox"/> 365 Personal Injury - Product Liability <input type="checkbox"/> 368 Asbestos Personal Injury Product Liability PERSONAL PROPERTY <input type="checkbox"/> 370 Other Fraud <input type="checkbox"/> 371 Truth in Lending <input type="checkbox"/> 380 Other Personal Property Damage <input type="checkbox"/> 385 Property Damage Product Liability	<input type="checkbox"/> 610 Agriculture <input type="checkbox"/> 620 Other Food & Drug <input type="checkbox"/> 625 Drug Related Seizure of Property 21 USC 881 <input type="checkbox"/> 630 Liquor Laws <input type="checkbox"/> 640 R.R. & Truck <input type="checkbox"/> 650 Airline Regs. <input type="checkbox"/> 660 Occupational Safety/Health <input type="checkbox"/> 690 Other LABOR <input type="checkbox"/> 710 Fair Labor Standards Act <input type="checkbox"/> 720 Labor/Mgmt. Relations <input type="checkbox"/> 730 Labor/Mgmt. Reporting & Disclosure Act <input type="checkbox"/> 740 Railway Labor Act <input type="checkbox"/> 790 Other Labor Litigation <input type="checkbox"/> 791 Empl. Ret. Inc. Security Act	<input type="checkbox"/> 422 Appeal 28 USC 158 <input type="checkbox"/> 423 Withdrawal 28 USC 157 PROPERTY RIGHTS <input type="checkbox"/> 820 Copyrights <input checked="" type="checkbox"/> 830 Patent <input type="checkbox"/> 840 Trademark SOCIAL SECURITY <input type="checkbox"/> 861 HIA (1395ff) <input type="checkbox"/> 862 Black Lung (923) <input type="checkbox"/> 863 DIWC/DIWW (405(g)) <input type="checkbox"/> 864 SSID Title XVI <input type="checkbox"/> 865 RSI (405(g)) FEDERAL TAX SUITS <input type="checkbox"/> 870 Taxes (U.S. Plaintiff or Defendant) <input type="checkbox"/> 871 IRS—Third Party 26 USC 7609	<input type="checkbox"/> 400 State Reapportionment <input type="checkbox"/> 410 Antitrust <input type="checkbox"/> 430 Banks and Banking <input type="checkbox"/> 450 Commerce <input type="checkbox"/> 460 Deportation <input type="checkbox"/> 470 Racketeer Influenced and Corrupt Organizations <input type="checkbox"/> 480 Consumer Credit <input type="checkbox"/> 490 Cable/Sat TV <input type="checkbox"/> 810 Selective Service <input type="checkbox"/> 850 Securities/Commodities/Exchange <input type="checkbox"/> 875 Customer Challenge 12 USC 3410 <input type="checkbox"/> 890 Other Statutory Actions <input type="checkbox"/> 891 Agricultural Acts <input type="checkbox"/> 892 Economic Stabilization Act <input type="checkbox"/> 893 Environmental Matters <input type="checkbox"/> 894 Energy Allocation Act <input type="checkbox"/> 895 Freedom of Information Act <input type="checkbox"/> 900 Appeal of Fee Determination Under Equal Access to Justice <input type="checkbox"/> 950 Constitutionality of State Statutes	
REAL PROPERTY <input type="checkbox"/> 210 Land Condemnation <input type="checkbox"/> 220 Foreclosure <input type="checkbox"/> 230 Rent Lease & Ejectment <input type="checkbox"/> 240 Torts to Land <input type="checkbox"/> 245 Tort Product Liability <input type="checkbox"/> 290 All Other Real Property	CIVIL RIGHTS <input type="checkbox"/> 441 Voting <input type="checkbox"/> 442 Employment <input type="checkbox"/> 443 Housing/Accommodations <input type="checkbox"/> 444 Welfare <input type="checkbox"/> 445 Amer. w/Disabilities - Employment <input type="checkbox"/> 446 Amer. w/Disabilities - Other <input type="checkbox"/> 440 Other Civil Rights	PRISONER PETITIONS <input type="checkbox"/> 510 Motions to Vacate Sentence Habeas Corpus: <input type="checkbox"/> 530 General <input type="checkbox"/> 535 Death Penalty <input type="checkbox"/> 540 Mandamus & Other <input type="checkbox"/> 550 Civil Rights <input type="checkbox"/> 555 Prison Condition			

V. ORIGIN (Place an "X" in One Box Only)						Appeal to District Judge from Magistrate Judgment
<input checked="" type="checkbox"/> 1 Original Proceeding	<input type="checkbox"/> 2 Removed from State Court	<input type="checkbox"/> 3 Remanded from Appellate Court	<input type="checkbox"/> 4 Reinstated or Reopened	<input type="checkbox"/> 5 Transferred from another district (specify)	<input type="checkbox"/> 6 Multidistrict Litigation	<input type="checkbox"/> 7

VI. CAUSE OF ACTION	Cite the U.S. Civil Statute under which you are filing (Do not cite jurisdictional statutes unless diversity): <u>35 U.S.C. § 271</u> Brief description of cause: <u>patent infringement</u>
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VII. REQUESTED IN COMPLAINT:	<input type="checkbox"/> CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23	DEMAND \$ _____	CHECK YES only if demanded in complaint: JURY DEMAND: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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VIII. RELATED CASE(S) IF ANY	(See instructions): JUDGE _____	DOCKET NUMBER _____
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DATE <u>May 22, 2008</u>	SIGNATURE OF ATTORNEY OF RECORD
FOR OFFICE USE ONLY	

RECEIPT # _____	AMOUNT _____	APPLYING IFP _____	JUDGE _____	MAG. JUDGE _____
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